A STUDY ON THE ASSOCIATION OF SERUM URIC ACID IN NEW AND RECENT ONSET PRIMARY HYPERTENSION

Dissertation submitted to
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
in partial fulfillment of the regulations
for the award of the degree of

M.D. BRANCH – I
GENERAL MEDICINE

K.A.P.V. GOVERNMENT MEDICAL COLLEGE, TIRUCHIRAPPALLI
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

MARCH – 2010

CERTIFICATE

This is to certify that the dissertation entitled "A STUDY ON THE ASSOCIATION OF SERUM URIC ACID IN NEW AND RECENT ONSET PRIMARY HYPERTENSION" is the bonafide original work of Dr. R. SARAVANAN in partial fulfillment of the requirements for M.D. Branch-I (General Medicine) Examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in March 2010.

Prof. Dr. P. KANAGA RAJ, ***M.D.,***
Associate Professor of Medicine,
Unit Chief,
K.A.P.V. Govt. Medical College,
Trichy – 1.

Prof. Dr. S. PANNEER SELVAM,*M.D.,*
Professor & Head of the
Department of Medicine,
K.A.P.V. Govt. Medical College,
Trichy – 1.

DEAN
K.A.P.V. Govt. Medical College,
Trichy – 1.

DECLARATION

I Dr. R. SARAVANAN, solemnly declare that dissertation titled, "A STUDY ON THE ASSOCIATION OF SERUM URIC ACID IN NEW AND RECENT ONSET PRIMARY HYPERTENSION" is a bonafide work done by me at K.A.P.V. Government Medical College, during 2007-2009 under the guidance and supervision of my Unit Chief Prof. Dr. P. KANAGA RAJ, M.D., Associate Professor of Medicine, Chief – Medical Unit – III.

The dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree (Branch – I) in General Medicine.

Place: Trichy

Date : **Dr. R. SARAVANAN**

ACKNOWLEDGEMENT

I owe my thanks to **Dr. S. Balasubramanian, M.D.,** THE DEAN, K.A.P.V. Govt. Medical College and Annal Gandhi Memorial Government Hospital, for allowing me to avail the facilities needed for my dissertation work.

I am grateful to **Prof. Dr. S. Panneer Selvam, M.D.,** Prof. and Head of the Department of Medicine, K.A.P.V. Govt. Medical College for permitting me to do the study and for his encouragement.

I express my gratitude to **Prof. Dr. P. Kanaga Raj, M.D.,** Associate Professor of Medicine and Chief of Medical Unit III, for his valuable assistance and guidance.

I express my gratitude to **Registrar / Prof. Dr. M. Sivasankaran, M.D.,** Department of Medicine and K.A.P.V. Govt. Medical College, for his valuable assistance and guidance.

I owe my thanks to **Prof. Dr. Selvapandian, M.D.,** Professor and Head of the Department of Biochemistry, K.A.P.V. Govt. Medical College for his help and guidance.

I am extremely thankful to **Dr. N. Sundar, M.D., Dr. C. Manoharan, M.D., Dr. N.K. Senthilnathan, M.D., Dr. D. Nehru, M.D., DMRD.,** Assistant Professors of Medicine, K.A.P.V. Govt. Medical College, who has been the inspiration behind this study and for their unlimited encouragement, guidance and help during this study.

I owe my thanks to **Dr. A.R. Parveen Gani, M.D.,** Associate Professor of Community Medicine, **Dr. S. Kandasamy, M.D., D.M.,** Assistant Professor of Medicine, **Dr. S. Rajasekaran, M.D., D.M.,** for their guidance and help during this study.

Last but not least, my sincere thanks to all the **patients** who co-operated for this study, without whom this study could not have been undertaken and to all my **colleagues** who helped me and shared their knowledge about this study.

Dr. Saravanan

CONTENTS

INTRODUCTION

CHAPTER – I

INTRODUCTION

Hypertension is an increasing important medical and public health issue. Hypertension markedly increases the risk for myocardial infarction, stroke, congestive heart failure, peripheral vascular disease and end stage renal disease.

Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension.[1] The WHO reports that suboptimal blood pressure (>115 mm Hg Systolic BP) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease, with little variation by sex. In addition, suboptimal blood pressure is the number one attributable risk for death throughout the world.[1]

Approximately 30% of adults are still unaware of their hypertension, more than 40% of individuals are not on treatment, and two thirds of hypertensive patients are not being controlled to BP levels less than 140/90 mm Hg.[1]

Studies of uric acid levels and the development of hypertension have generally been consistent, continuous, and of similar magnitude. Hyperuricemia is also common among adults with prehypertension, especially when microalbuminuria is present[1]. The observation that

hyperuricemia precedes the development of hypertension indicates that it is not simply a result of hypertension per se.[2]

Uric acid is a purine metabolite that in most mammals is degraded by the hepatic enzyme uricase to allantoin. However, mutations in the uricase gene occurred during primate development, with the consequence that humans have relatively higher levels of serum uric acid.

An elevation in serum uric acid has been associated with an increased risk for the development of hypertension,[4,6] and 25% to 50% of hypertensive individuals are hyperuricemic[6]. Hyperuricemia also confers increased risk for cardiovascular mortality, especially in women.[6,7] Despite the clinical and epidemiological evidence, many authorities do not consider an elevated uric acid to be a true cardiovascular risk factor, because patients with hyperuricemia often have other well-established risk factors for cardiovascular disease, such as hypertension, renal disease, obesity, dyslipidemia, and insulin resistance.

Several studies have found that an elevated uric acid level is an independent risk factor for cardiovascular disease after controlling for the contribution of established risk factors by multivariate analyses. The lack of a mechanism by which uric acid can cause cardiovascular disease, coupled with the inconclusive clinical and epidemiological data, has left the issue unresolved.

AIM OF THE STUDY

CHAPTER – II

AIM OF THE STUDY

Numerous studies have reported that hyperuricemia carries an increased relative risk for hypertension, independent of other risk factors. The aim of this study is

1. To find the association of hyperuricemia in new-onset and recent onset Hypertensive patients.
2. To find the association of hyperuricemia in hypertensive patients with regard to gender and risk factors like smoking, central obesity and BMI.
3. To find the association of serum uric acid in hypertensive patients who have metabolic syndrome.

REVIEW OF LITERATURE

CHAPTER – III

REVIEW OF LITERATURE

Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. Hypertension is often associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of risk factors.[10]

MECHANISMS OF HYPERTENSION

1. INTRAVASCULAR VOLUME

The initial elevation of blood pressure in response to vascular volume expansion is related to an increase of cardiac output; however, over time, peripheral resistance increases and cardiac output reverts toward normal.

The mechanism for the “pressure-natriuresis” phenomenon may involve a subtle increase of glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor.[10]

AUTONOMIC NERVOUS SYSTEM

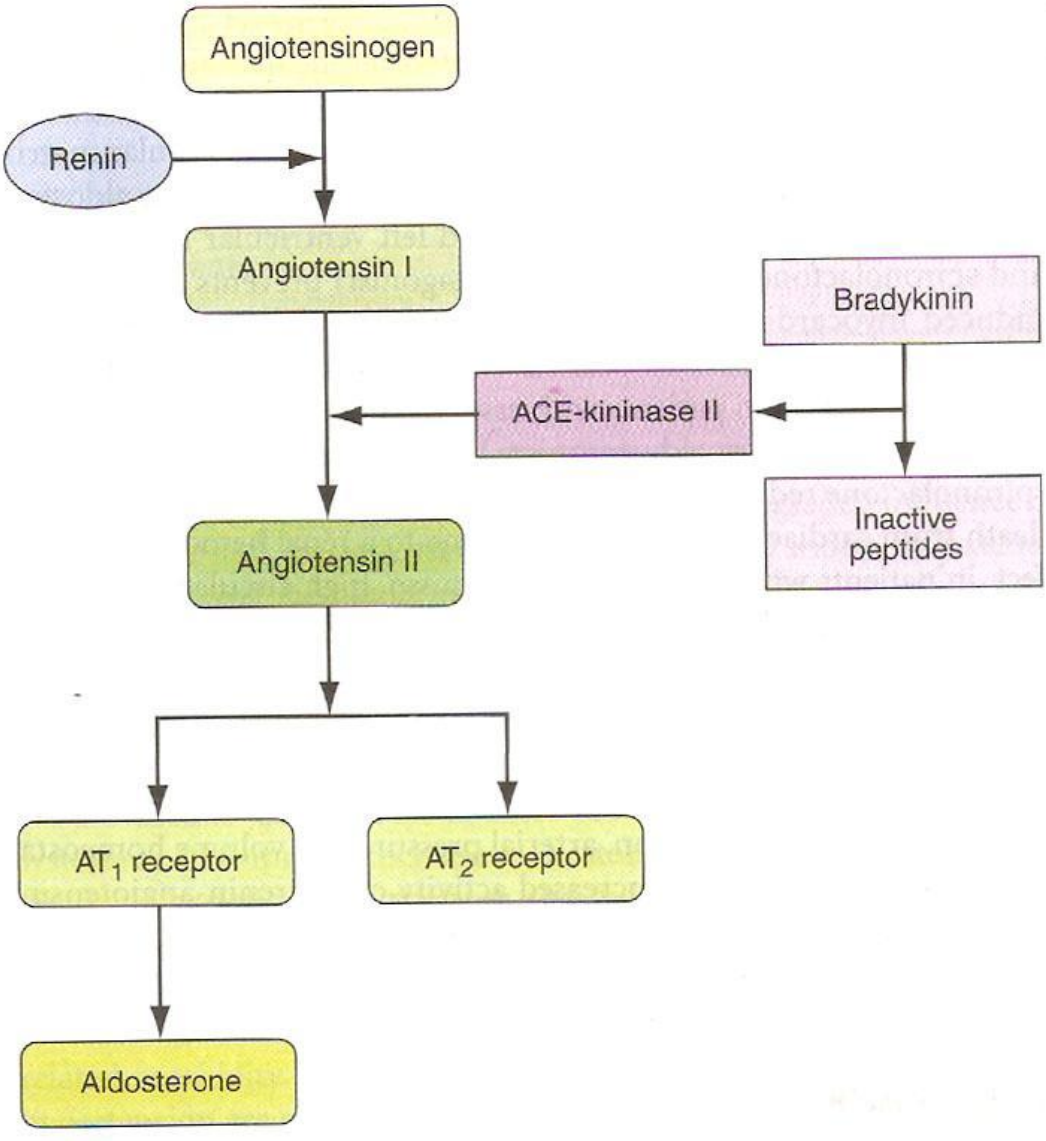
The autonomic nervous system maintains cardiovascular homeostasis via pressure, volume and chemoreceptor signals. Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure.[10]

RENIN-ANGIOTENSIN-ALDOSTERONE-SYSTEM

The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. Angiotensin II is a potent pressor substance, the primary trophic factor for the secretion of aldosterone by the adrenal zona glomerulosa, and a potent mitogen stimulating vascular smooth-muscle cell and myocyte growth. Independent of its hemodynamic effects, Angiotensin II may play a role in the pathogenesis of atherosclerosis through a direct cellular action on the vessel wall.[10]

Aldosterone also has effects on nonepithelial targets. Independent of a potential effect on blood pressure, aldosterone may also play a role in cardiac hypertrophy and CHF.

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM



Pathologic patterns of left ventricular geometry have also been associated with elevations of plasma aldosterone concentration in patients with essential hypertension, as well as in patients with primary aldosteronism.

PATHOLOGIC CONSEQUENCES OF HYPERTENSION

1. HEART

Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, diastolic dysfunction, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease and cardiac arrhythmias.

Diastolic dysfunction is an early consequent of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia.

2. BRAIN

Hypertension is an important risk factor for brain infarction and hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years.[10]

Hypertension is also associated with impaired cognition in an aged population. Hypertensive encephalopathy is related to failure of

autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion. Untreated hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours.

3. KIDNEY

Hypertension is a risk factor for renal injury and ESRD. The increased risk associated with high blood pressure is graded, continuous, and present throughout the entire distribution of blood pressure above optimal. Renal risk appears to be more closely related to systolic than to diastolic blood pressure.

The atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect the preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic.

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio > 300 μg/mg) or microalbuminuria (a random urine albumin / creatinine ratio 30-300 μg/mg) are early markers of renal injury.[10]

4. PERIPHERAL ARTERIES

Hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. The ankle-brachial index is a useful approach for evaluating Peripheral Arterial Disease and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood pressure. An ankle-brachial index < 0.90 is considered diagnostic of Peripheral Arterial Disease.

DEFINING HYPERTENSION

From an epidemiologic perspective, there is no obvious level of blood pressure that defines hypertension. The multiple Risk Factor Intervention Trial (MRFIT), which included > 350,000 male participants, demonstrated a continuous and graded influence of both systolic and diastolic blood pressure on CHD mortality.

Cardiovascular disease risk doubles for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic pressure. Among older individuals, systolic blood pressure and pulse pressure are more powerful predictors of cardiovascular disease than diastolic blood pressure.[1,10]

CRITERIA

Recommended criteria for a diagnosis of hypertension are average awake blood pressure ≥ 135/85 mmHg and asleep blood pressure

≥ 120/75 mmHg. These levels approximate a clinic blood pressure of ≥ **140/90 mm Hg**.[1,10]

Classification of Blood Pressure for Adults

Based on the seventh report of **JOINT NATIONAL COMMITTEE** ON PREVENTION, DETECTION, EVALUATION AND TREATMENT OF HYPERTENSION (JNC 7).

Table – 1

JNC VII Classification

Blood Pressure Classification	Systolic, mmHg	Diastolic, mmHg
Normal	< 120	and < 80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥ 160	or ≥ 100
Isolated systolic hypertension	≥ 140	and ≤ 90

ACCURATE BLOOD PRESSURE MEASUREMENT

The accurate measurement of BP is the sine qua non for successful management. The equipment, whether aneroid, mercury, or electronic, should be trained and regularly retrained in the standardized technique, and the patient must be properly prepared and positioned. The auscultatory method of BP measurement should be used.

Persons should be seated quietly for at least 5 minutes in a chair (rather than on an examination table), with feet on the floor, and arm supported at heart level. Caffeine, exercise and smoking should be avoided for at least 30 minutes prior to measurement. Measurement of BP in the standing position is indicated periodically, especially in those who report symptoms consistent with reduced BP on standing. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least two measurements should be made and the average recorded.

For manual determinations, palpated radial pulse obliteration pressure should be used to estimate SBP; the cuff should then be inflated 20 to 30 mm Hg above this level for the auscultatory determinations; the cuff deflation rate for auscultatory readings should be 2 mm Hg per second. SBP is the point at which the first of two or more Korotkoff sounds is heard (onset of phase 1), and the disapperance of Korotkoff sound (onset of phase 5) is used to define DBP.

In certain conditions like Aortic Regurtitation, the diastolic BP will be 0 mm Hg and the appearance of muffled sound is taken as diastolic BP. Care should be taken while measuring BP in elderly patients as there will be auscultatory gap.

Recommendations for Follow-Up Based on Initial Blood Pressure Measurements for Adults without Acute End Organ Damage (JNC-7)

Initial Blood Pressure, mm Hg*	Follow-Up Recommended+
Normal	Recheck in 2 years
Prehypertension	Recheck in 1 year
Stage 1 Hypertension	Confirm within 2 months#
Stage 2 Hypertension	Evaluate or refer to source of care within 1 month. For those with higher pressures (eg, > 180/110 mm Hg), evaluate and treat immediately or within 1 week depending on clinical situation and complications.

* If systolic and diastolic categories are different, follow recommendations for shorter time follow-up (e.g, 160/86 mm Hg should be evaluated or referred to source of care within 1 month).

\+ Modify the scheduling of follow-up according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.

\# Provide advice about lifestyle modifications.

The key messages of JNC – VII are:[(1)]

- In those older than age 50, systolic blood pressure of greater than 140 mm Hg is a more important cardiovascular disease (CVD) risk factor than diastolic BP.
- Beginning at 115/75 mm Hg, CVD risk doubles for each increment of 20/10 mm Hg.
- Those who are normotensive at 55 years of age will have a 90% life time risk of developing hypertension.

- Ø Prehypertensive individuals require health promoting lifestyle modifications to prevent the progressive rise in blood pressure and Cardio Vascular Disease.
- Ø For uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most patients, either alone or combined with drugs from other classes.
- Ø Two or more antihypertensive drugs will be required to achieve goal BP (<140/90 mm Hg or <130 mm Hg) for patients with diabetes and chronic kidney disease.
- Ø For patients whose BP is more than 20 mm Hg above the systolic BP goal or more than 10 mm Hg above the diastolic BP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered.

CLINICAL DISORDERS OF HYPERTENSION

1. ESSENTIAL HYPERTENSION
2. METABOLIC SYNDROME
3. RENOVASCULAR HYPERTENSION
4. PRIMARY ALDOSTERONISM
5. CUSHING'S SYNDROME
6. PHEOCHROMOCYTOMA

7. MISCELLANEOUS CAUSES OF HYPERTENSION

Obstructive sleep apnea, Coarctation of the aorta, acromegaly, hypercalcemia, both hypo and hyper thyroidism.

8. MONOGENIC HYPERTENSION

ESSENTIAL HYPERTENSION

Essential hypertension tends to be familial and is likely to be the non-sequence of an interaction between environmental and genetic factors. The prevalence of essential hypertension increases with age. In the majority of patients with established hypertension, peripheral resistance is increased and cardiac output is normal or decreased; however, in younger patients with mild or labile hypertension, cardiac output may be increased and peripheral resistance may be normal.

High-renin patients may have a vasoconstrictor form of hypertension, whereas low-renin patients may have a volume-dependent hypertension.[(10)]

URIC ACID METABOLISM

Uric acid is the final breakdown product of purine degradation in humans. Urates, the ionized forms of uric acid, predominate in plasma extracellular fluid and synovial fluid, with ~98% existing as monosodium urate at pH 7.4.[11]

The pH of urine greatly influences the solubility of uric acid. Although purine nucleotides are synthesized and degraded in all tissues, urate is produced only in tissues that contain xanthine oxidase, primarily the liver and small intestine. Urate production varies with the purine content of the diet and the rates of purine biosynthesis, degradation, and salvage. Normally, two-third to three-fourth of urate is excreted by the kidney, and most of the remainder is eliminated through the intestine.

METABOLISM

The kidneys clear urate from the plasma and maintain physiologic balance by utilizing specific organic anion transporters (OATs) including urate transporter 1 (URATI) and human uric acid transporter (hUAT). URAT1and other OATs carry urate into the tubular cells from the apical side of the lumen. Once inside the cell, urate must pass to the basolateral side of the lumen in a process controlled by the voltage-dependent carrier

hUAT. Until recently, component model has been used to describe the renal handling of urate / uric acid. The methods are

(1) Glomerular filtration,

(2) Tubular reabsorption

(3) Secretion, and

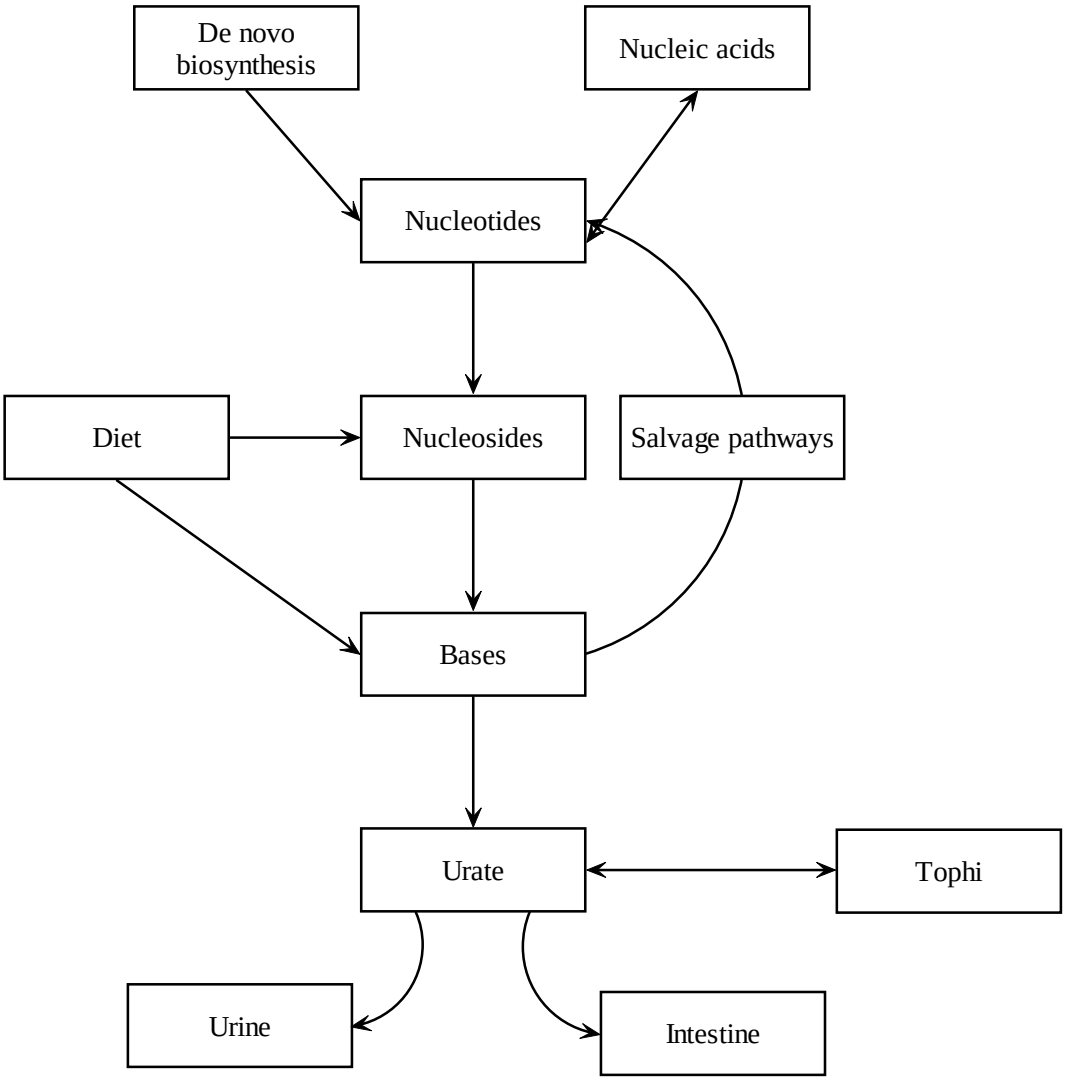
(4) Postsecretory reabsorption.

URAT1 is a novel transporter expressed at the apical brush border of the proximal nephron. Uric acid compounds directly inhibit URAT1 on the apical side of the tubular cell (so-called cis-inhibition).[11]

The total-body urate pool is the net result between urate production and excretion

Urate production is influenced by dietary intake of purines and the rates of de novo biosynthesis of purines from nonpurine precursors, nucleic acid turnover, and salvaging phosphoribosyltransferase activities. The formed urate is normally excreted by urinary and intestinal routes. Hyperuricemia can be caused by increased production, decreased excretion, or a combination of mechanisms. When hyperuricemia exists, urate can precipitate and deposit in tissues as tophi.

URIC ACID TURNOVER AND METABOLISM



HYPERURICEMIA

Hyperuricemia is defined as a plasma (or serum) urate concentration > 6.0mg/dl in females and > 7.0mg/dl in males.[2,11,12]

CAUSES OF HYPERURICEMIA

Hyperuricemia may be classified as primary or secondary depending on whether the cause is innate or is the result of an acquired disorder.

However, it is more useful to classify hyperuricemia in relation to the underlying pathophysiology, i.e., whether it results from increased production, decreased excretion, or a combination of the two.

Classification of hyperuricemia by pathophysiology

Urate Overproduction		
Primary idiopathic	Myeloproliferative diseases	Rhabdomyolysis
HPRT deficiency	Polycythemia vera	Exercise
PRPP synthetase Overactivity	Psoriasis	Alcohol
Hemolytic processes	Paget's disease	Obesity
Lymphoproliferative diseases	Glycogenosis III, V, and VII	Purine-rich diet
Decreased Uric Acid Excretion		
Primary idiopathic	Starvation ketosis	Drug ingestion
Renal insufficiency	Berylliosis	Salicylates (> 2 g/d)
Polycystic kidney disease	Sarcoidosis	Diuretics
Diabetes insipidus	Lead intoxication	Alcohol
Hypertension	Hyperparathyroidism	Levodopa
Acidosis	Hypothyroidism	Ethambutol
Lactic acidosis	Toxemia of pregnancy	Pyrazinamide
Diabetic ketoacidosis	Bartter's syndrome	Nicotinic acid
Down syndrome	Cyclosporine	
Combined Mechanism		
Glucose-6-phosphatase deficiency	Fructose-1-phosphate aldolase deficiency	Alcohol
		Shock

Note: HPRT, hypoxanthine phosphoribosyltransferase, PRPP, phosphoribosylpyrophosphate.

HISTORY OF URIC ACID AND HYPERTENSION

The concept that uric acid may be involved in hypertension is not a new one. In fact, in the paper published in 1879 that originally described essential hypertension, Frederick Akbar Mohamed noted that many of his subjects came from gouty families. He hypothesized that uric acid might be integral to the development of essential hypertension.[13]

Ten years later, this hypothesis reemerged when Haig[14] proposed low-purine diets as a means to prevent hypertension and vascular disease. In 1909, the French academician Henri Huchard noted that renal arteriolosclerosis (the histologic lesion of hypertension) was observed in three groups: Those with gout, those with lead poisoning, and those who have a diet enriched with fatty meat. All of these groups are associated with hyperuricemia.[15]

The association between elevated serum uric acid and hypertension was observed and reported repeatedly in the 1950s to 1980 but received relatively little sustained attention because of the lack of a mechanistic explanation.[16-18]

Twenty-five to 40% of adult patients with hypertension have hyperuricemia (> 6.5 mg/dl), and this number increases dramatically when serum uric acid in the high-normal range is included.[19,20] In pre-eclampsia, the correlation between elevated serum uric acid and

hypertension is > 70%.[21] Despite these observations, the lack of a causal mechanism led to mild elevations of serum uric acid being largely ignored in medical practice.

The strength of the relationship between uric acid level and hypertension decreases with increasing patient age and duration of hypertension, suggesting that uric acid may be most important in younger subjects with early-onset hypertension. [18]

Cross-sectional studies have consistently noted that more than a quarter of patients with untreated hypertension have elevated serum UA.[19,22] Serum UA levels have also been associated cross-sectionally with BP[18,23,24] and longitudinally with hypertension incidence [4,5,27-29] and future increases in BP.[30]

Mild hyperuricemia in the Rat, an animal model for essential hypertension

The study of mild hyperuricemia required an animal model before the lack of any mechanistic detail that had plagued the hypothesis over 100 years could be addressed.

In the late 1990s, Johnson and Colleagues[31] developed a model using a pharmacologic inhibitor of urate oxidase, oxonic acid, that allows the study of sustained mild hyperuricemia. When fed 2% oxonic acid in their standard diet, Sprague-Dawley rats have an increase of mean serum

uric acid concentrations from 0.5 to 1.4 g/dl to 1.7 to 3.0 mg/dl. During a 7-wk treatment period, systolic BP increases an average of 22 mmHg. The increase in BP can be prevented entirely by the co-administration of the xanthine oxidase inhibitor allopurinol or by the uricosuric agent benziodarone, indicating linearly related to the rise in uric acid ($r = 0.77$).

Histologic evaluation of the renal tissue of the hyperuricemic, hypertensive rats reveals an expansion of the vascular smooth muscle and narrowing of the lumina of the afferent arterioles. It is interesting that the development of arteriolosclerosis can be prevented using allopurinol to control uric acid levels; however, hydrochlorothiazide, which normalizes BP without lowering serum uric acid, does not prevent the development of arteriolosclerosis, indicating that uric acid, not hypertension, is the causative stimulus.[22,32]

These experimental results indicate that mild hyperuricemia induces renal inflammation, activation of the renin-angiotensin system, and downregulation of nitric oxide production, all of which are potentially important pathways that lead to uric acid-mediated hypertension.

In short, mild hyperuricemia leads to an irreversible salt-sensitive hypertension over time.

Recent in vitro studies also have elucidated the possible mechanism of uric acid-mediated arteriolosclerosis. Primary human vascular smooth muscle cells (HVSMC) are induced to proliferate by addition of uric acid to the growth medium in a dose-dependent manner.[33] The human smooth muscle cells express the urate-transport channel URAT1 as evidenced by both Northern and Western analyses. Consistent with this observation, cultured HVSMC rapidly take up C-urate, and blockade of this uptake by probenecid attenuates the uric acid-mediated induction of proliferation in a dose-dependent manner.[34] Signaling studies have revealed further the possible mechanism by which urate uptake leads to HVSMC proliferation.[33,35,36]

The effect of uric acid on vascular smooth muscle cells (VSMC)

Uric acid is taken up through the probenecid-sensitive urate-transport channel URAT1. This leads to mitogen-activated protein kinase activation and extracellular signal-regulated kinase 1 and 2 (Erk ½) Phosphorylation. In turn, transcription factors NF-β (nuclear transcription factor) and AP1 are activated leading to increased cyclo-oxygenase-2 (COX-2) expression and activity. The COX-2 product Thromboxane A_2 mediates increased expression and elaboration of platelet derived growth factor (PDGF) and monocyte chemoattractant protein-1 (MCP-1), which

induce VSMC proliferation and macrophage infiltration, respectively.[33,35,36]

REMNANT KIDNEY MODEL

Various studies have investigated the effect of uric acid on multiple mechanisms of progressive renal injury. In the remnant kidney model, Hyperuricemic remnant kidney rats (caused by addition of 2% oxonic acid to their diets) had higher BP, greater proteinuria, and higher serum creatinine.[37,38] Addition of oxonic acid to cyclosporine treatment led to higher uric acid levels, more severe arteriolar hyalinosis, macrophage infiltration, and tubulointerstitial damage compared with rats that were treated with cyclosporine alone.[39] Furthermore treatment of cyclosporine-exposed rats with allopurinol improves GFR[39], and in human liver transplant patients who were receiving cyclosporine, treatment with allopurinol resulted in improved renal function.[40]

RECENT EPIDEMIOLOGY: A CHANGE IN PERSPECTIVE

Before 1990, only Khan et al.[27] had reported that an increased serum uric acid is an independent risk factor for hypertension; however, it had been noted that 25 to 40% of adults with hypertension have serum uric acid > 6.5 mg/dl and >60% have a serum uric acid > 5.5 mg/dl[19,20] and that there was a linear relationship between serum uric acid and

systolic BP.[41] Three reports indicated that serum uric acid is an independent risk factor for hypertension were published in the 1990s[25,26,29] and five more were published in the past 4 yrs[28,30,42,43,44], including two in the first month of 2005 (Table 2). The recent evaluation of a subset of the Framingham Heart Study found that serum uric acid level was an independent predictor of hypertension and BP progression over as little as 4 yrs.[44]

Uric acid and essential hypertension in children

In adolescents, the association between elevated serum uric acid and the onset of essential hypertension is even more striking. The Moscow Children's Hypertension study found hyperuricemia (> 8.0 mg/dl) in 9.5% of children with normal BP, 49% of children with borderline hypertension, and 73% of children with moderate and severe hypertension.[45]

The Hungarian Children's Health Study followed all 17,624 children who were born in Budapest in 1964 for 13yrs and found that significant risk factors for the development of hypertension were elevated heart rate, early sexual maturity, and hyperuricemia.[46]

Gruskin[47] compared adolescents (13 to 18yrs of age) who had essential hypertension with age-matched healthy control subjects and who

had normal BP. The hypertensive children had both elevated serum uric acid (mean > 6.5 mg/dl) and higher peripheral renin activity.

Feig and Johnson observed that the mean serum uric acid level (±SD) in control subjects and children with white coat hypertension were nearly identical but slightly higher in secondary hypertension (4.3 ± 1.4 mg/dl, respectively; P = 0.80) but very high in children with primary hypertension (6.7 ± 1.3 mg/dl; P = 0.004) [38]. There was a tight, linear correlation between the serum uric acid levels and the systolic and diastolic BP in patients who were referred for evaluation of hypertension (r = 0.8 for systolic BP and r = 0.6 for diastolic BP).[24]

Among patients who were referred for evaluation of hypertension, a serum uric acid > 5.5 mg/dl had an 89% positive predictive value for essential hypertension, whereas a serum uric acid level <5.0 had a negative predictive value for essential hypertension of 96%.[24]

The results from both animal and human studies strongly implicate uric acid as a factor in the onset of essential hypertension and as a potential contributor to the progression of renal injury.

Evidence linking uric acid and hypertension

1. An elevated uric acid level consistently predicts the development of hypertension.[25-29]

2. An elevated uric acid level is observed in 25-60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset.[24]
3. Raising the uric acid level in rodents results in hypertension with the clinical, hemodynamic, and histologic characteristics of hypertension.[31]
4. Reducing the uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset.[48]

MECHANISM OF HYPERTENSION IN HYPERURICEMIA - RAT MODEL

Most mammals have a low serum uric acid level because of the presence of uricase, a hepatic enzyme that degrades uric acid to allantoin. However in humans the uricase gene is mutated resulting in uric acid levels that are both higher and less regulatable than in other mammals. Interestingly when mild hyperuricemia was induced in rats by the administration of a uricase inhibitor, they became hypertensive.

Hypertension in this model was mediated by 2 mechanisms.

1. Uric acid induced renal vasoconstriction mediated by endothelial dysfunction with reduced NO levels and by activation of the renin-angiotensin system. This hypertension type is salt-resistant in that it

occurs even in the presence of a low-salt diet, and it responds to lowering of uric acid.

2. Later, however, the hyperuricemia causes progressive renal microvascular disease (a lesion resembling arteriolosclerosis), and once sufficient narrowing of the arteriolar lumen occurs, a component of the hypertension becomes salt-driven, renal-dependent, and independent of uric acid levels.

The identification of a biological mechanism by which uric acid could cause hypertension in humans has led to a renewed interest in the role of uric acid in hypertension. Indeed, there are now 10 studies that have examined whether an elevated uric acid level predicts the development of hypertension, and all found uric acid predictive.

The Bogalusa Heart study, found that uric acid levels in childhood predict the development of diastolic hypertension 10 years later. The second study, from the Framingham group[44], also found uric acid to predict the development of hypertension. This latter study is all the more remarkable as it was performed in an older population (mean age 50) in which they first eliminated 25% of their subjects because they already had hypertension or gout, thereby removing a large proportion of their target population.

PROPOSED MECHANISM FOR URIC ACID MEDIATED HYPERTENSION IN HUMANS[2]

Excessive intake of fructose or purine-rich meats or exposure to low doses of lead may result in chronic hyperuricemia. Mothers with high uric acid levels that are the result of diet or conditions such as preexisting hypertension, obesity, or preeclampsia may transfer uric acid into the fetal circulation through the placenta, which may ultimately contribute to intrauterine growth retardation (IUGR) and a reduction in nephron number. Among babies born with a low nephron number, hyperuricemia may develop in childhood because of genetic or environmental factors. Chronic hyperuricemia would stimulate the renin-angiotensin system and inhibit release of endothelial nitric oxide contributing to renal vasoconstriction and possibly increasing blood pressure. Persistent renal vasoconstriction may contribute to arteriolosclerosis and the development of salt-sensitive hypertension, even if the hyperuricemia is corrected.

PROPOSED MECHANISM FOR URIC ACID MEDIATED HYPERTENSION IN HUMANS [2]

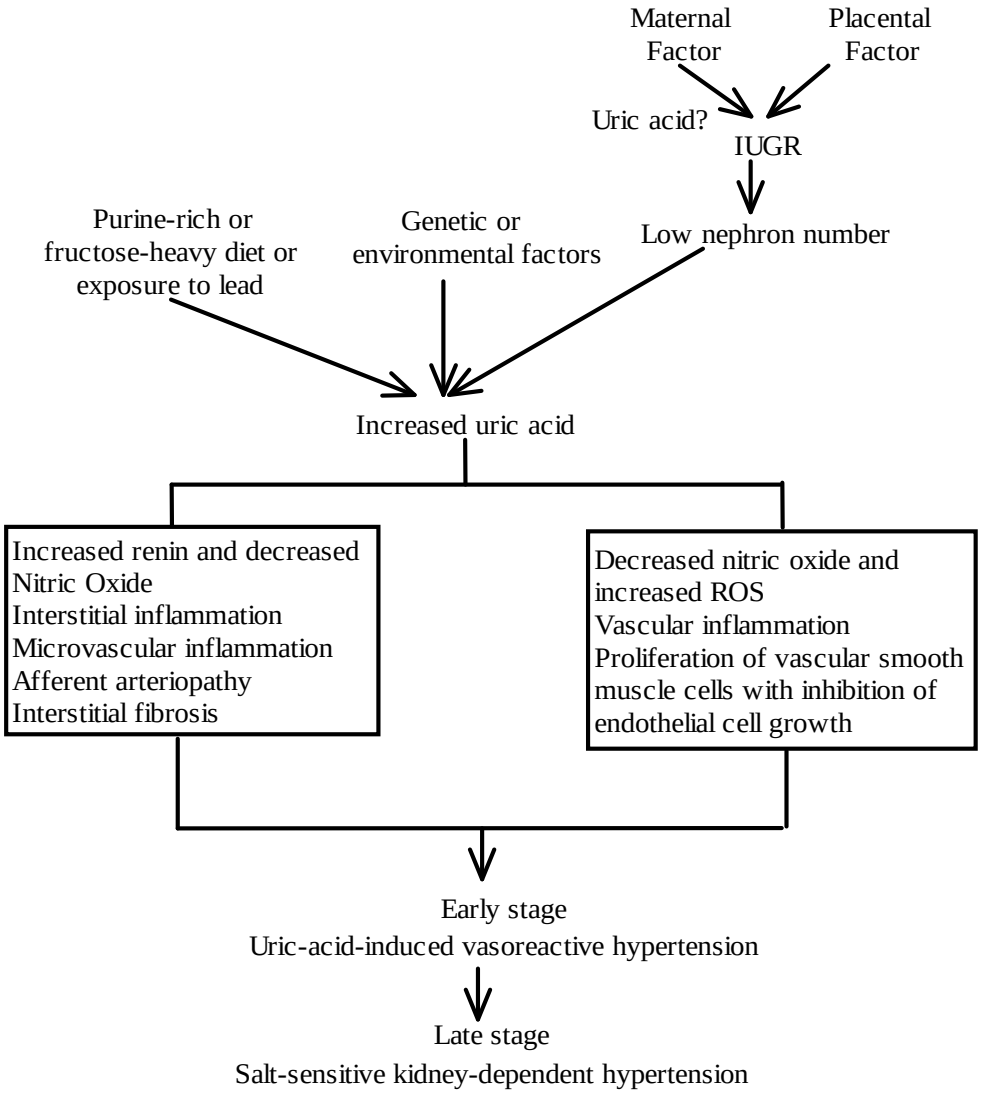


Table - 2

Epidemiological studies suggested that serum uric acid predicts hypertension

Author	Year published	Study size	Duration of Follow-up (yr)	Increased Risk
Kahn et al.[27]	1972	10,000 men	5	2-fold
Selby et al.[26]	1990	2062 adults	6	3-fold
Hunt et al.[29]	1991	1482 adults	7	2-fold
Jossa et al.[25]	1994	619 men	12	1.2-fold
Taniguchi et al.[42]	2001	6356 men	10	2-fold
Masuo et al.[30]	2003	433 men	5	+27 mmHg in systolic BP per each 1-mg/dl change in uric acid
Nakanishi et al.[28]	2003	2310 men	6	1.6-fold
Nagahama et al.[49]	2004	4489 adults	23	1.5-fold in men
Alper et al.[43]	2005	577 children	11	Predicts diastolic hypertension
Sundstrom et al.[44]	2005	3119 adults	4	1.5-fold

MATERIALS AND METHODS

CHAPTER – IV

MATERIALS AND METHODS

Study Setting

Annal Gandhi Memorial Government Hospital and K.A.P. Viswanatham Government Medical College, Trichy. The collaborative department was Department of Biochemistry, K.A.P. Viswanatham Government Medical College.

Study design

Analytical study.

Period of study

October 2008 to September 2009.

Ethical Committee Approval

The study was approved by the Ethical Committee, Trichy.

Patient Population

Cases

One hundred adults aged between 20-50 years were selected for the study and referred consecutively to the Hypertension OPD of Annal

Gandhi Memorial, Government Hospital, Trichy. They were studied for Serum Uric acid levels.

Controls

Normotensive controls (n = 100) were selected for the study and evaluated for clinical and laboratory data.

Both males and females were included for the study. All subjects and controls had normal renal function (Renal biochemistry, USG Abdomen).

Inclusion Criteria

1. Hypertensive patients, whom are of new-onset and recent onset (<1 yr) without any target end organ damage.
2. Age group between 20 to 50 years.
3. Both sexes were included.
4. Stage 1 and stage 2 Hypertension according to JNC-VII.

Exclusion Criteria

1. Hypertensive patients with Target End Organ damage
    1. Hypertensive Heart disease as evidenced by Left Ventricular hypertrophy - ECG-voltage criteria.
    2. Hypertensive Nephropathy

3. Hypertensive Retinopathy

2. Diabetes Mellitus – Type 1 and Type 2 or metabolic syndrome
3. Patients with Chronic kidney disease.
4. Hypertensive Patients with known Cerebro vascular disease.
5. Hypertensive Patients with coronary Artery disease - Myocardial Ischemia or Infarction.
6. Patients with long term drug intake like steroids, Anti-Tuberculous Treatment (ATT), diuretics, antimetabolite or chemotherapy drugs.
7. Patients who were regularly consuming alcohol – Alcohol dependence subjects - Evidenced by History, liver function tests and USG Abdomen.
8. Patients of Lympho or Myelo proliferative disorders.
9. Patients who had chronic liver disease and metabolic disorders.
10. Endocrine disorder – Hypothyroid patients.
11. Psoriasis patients.
12. Patients in whom BMI >30.
13. Hypertensive crisis / Malignant Hypertension

Consent

The study groups identified by the above criteria (inclusion and exclusion) were first informed about the nature of the study. Participants

willing for the study were selected after getting an informed and written consent from them.

Thus, a total of 100 patients were taken up for study who satisfied the inclusive and exclusion criteria. Similarly, 100 age and sex matched subjects were kept as control.

There was no conflict of interest and financial support was Nil.

Urinary excretion and urate clearance were not done, only serum uric acid levels were analysed.

Patient profile

Selected socio-demographic, clinical and laboratory data were collected from the cases and controls and recorded in proforma.

1. Socio-demographic profile

- Age
- Sex
- Occupation.
- Cardiovascular risk factors – smoking, family history

2. Clinical profile

- Body weight
- Height

- Body mass index
- Waist circumference
- Pulse
- Systolic and diastolic blood pressure – Average of 2 BP measurements
- Clinical examination

Evaluation of subject and controls

Laboratory analyses, performed in Biochemical laboratory at the AGM Government Hospital, Trichy included blood tests for the evaluation of renal parameters, fasting blood sugar, serum electrolytes, uric acid, lipid profile, thyroid function tests.

- Complete urinalyses were performed by the pathological faculty.
- ECG was taken for all the subjects and controls to rule out coronary artery disease and left ventricular hypertrophy.
- Fundus examination was done for all subjects.

Definitions used in the present study

1. Hypertension

Hypertension is defined as systolic blood pressure of ≥ 140mmHg or diastolic blood pressure ≥ 90 mmHg.

Blood pressure classification: By JNC VII

Normal	Systolic, mm Hg	Diastolic mm Hg
Pre hypertension	120-139	or 80-89
Stage 1	140-159	or 90 – 99
Stage 2	≥ 160	or ≥ 100
Isolated systolic hypertension	≥ 140	and < 90

2. Hyperuricemia

Hyperuricemia is defined as serum uric acid level more than > 7.0 mg/dl in Indian men and > 6.0mg/dl in Indian women. [2,11,12]

3. Body Mass Index

It is calculated by using the following formula

$$= \frac{\text{weight kg}}{\text{Height in metres}^2}$$

4. Waist circumference

The waist is measured by taking a circumference that gives the narrowest measurement between the rib cage and the iliac crest. It is an important component of the diagnostic criteria for the metabolic syndrome. It is a simple, convenient and reliable marker for intra abdominal fat and total body fat.

Central obesity

According to NCFP: ATP III (National Cholesterol) Education program Adult Treatment Panel III)

Waist circumference > 102 cm in males > 88 cm in females.

Body Mass Index > 30, is usually classified as obesity. Body mass index between 25 to 30 should be viewed as medically significant, especially in the presence of other risk factors like hypertension, diabetes. Large scale epidemiological studies suggest that cardiovascular morbidity begins to rise when body mass index > 25, suggesting that the cut off for obesity should be lowered.

5. Metabolic syndrome

NCEP: ATP III 2001.

Three or more of the following:

1. Central obesity

   Waist circumference >102 cm (m) > 88cm (F)

2. Hypertriglyceridemia

   Triglycerides ≥ 150mg / dl or specific medication.

3. Low HDL cholesterol: < 40 mg / dl (M) and < 50 mg / dl (F) or specific medication.

4. Hypertension: Blood pressure ≥ 130 mm Hg systolic BP or ≥ 85 mm Hg diastolic BP or specific medication.
5. Fasting plasma glucose ≥100 mg/dl or specific medication or previously diagnosed type 2 diabetes.

Laboratory Data

- Blood urea estimation was done manually by using urease GLDH (Glutamate and Lactate De-Hydrogenase) method.
- Serum creatinine estimation was done by using modified Jaffes method and calibrated by fully automated random access Biochemistry analyzer XL 300.
- Serum uric acid was done by using uricase method and calibrated by fully automated random access Biochemistry analyzer XL 300.
- Blood Glucose was estimated by using GOD / POD (Glucose oxidase and peroxidase) method and estimated by ERBA auto analyzer.

Principle of Uric acid estimation

Uric acid is converted by uricase to allantoin and hydrogen peroxide in the presence of peroxidase, oxidizing the chromogen to a red coloured compound which is read at 500 nm.

1) Uric acid + $2H_2O + O_2 \xrightarrow{\text{uricase}}$ Allantoin + $CO_2 + H_2O_2$.

2) $2H_2O_2$ + 4 Aminopyrine $\xrightarrow{\text{DHBSPeroxidase}}$ Red Quinolone + H_2O + HCl

(DHBS – 3,5 – Dichloro – 2-Hyroxy Benzene Sulphonic acid)

Statistical Analysis

Data was entered in Microsoft excel spread sheet and analyzed statistically using standard statistical software. Significance testing of the difference between means was done by unpaired 2 – tailed **student 't' test**, and correlations were assessed by Pearson coefficient. Significance was considered, if the 'p' value was below 0.05.

OBSERVATIONS AND RESULTS

CHAPTER – V

OBSERVATIONS AND RESULTS

The total number of subjects included in this study was 200. Of these 100 were study cases (Hypertensive without target end organ damage) and another 100 were controls (Non – Hypertensive).

Both the cases and controls selected were adjusted for age distribution, Sex, BMI, selected cardio vascular risk factors like smoking, family history.

At the end of the study, 30 subjects in study group were found to have metabolic syndrome according to NCEP : ATP III criteria. Similarly 10 of the 100 controls satisfied the criteria for metabolic syndrome.

Both the cases and controls whom had met the criteria for metabolic syndrome were excluded from the study.

Many studies previously published had indicated that hyperuricemia is also associated with metabolic syndrome, as other conditions like coronary artery disease, stroke, pre eclampsia, malignant hypertension and chronic kidney disease.

Thus, subjects selected for the study after excluding metabolic syndrome were: **Cases – 70; Controls – 90**

Table – 1

Selected Subjects for the study

Metabolic Syndrome	Cases	Controls
+	30	10
-	70	90
Total	100	100

Subjects finally selected
Cases – 70 Controls – 90

Distribution of Socio-demographic and clinical profile in cases and controls

Table – 2

S. No.		Cases	Controls
1.	Total	70	90
2.	Gender	M = 43; F = 27	M = 52; F = 38
3.	Mean Age	37.34	37.21
4.	BMI	20.96 to 30.00	20.59 to 29.38
5.	Mean BMI	25.07	24.99
6.	Waist Circumference	82 – 106 cms.	80 – 106 cms.
7.	Blood Pressure		
	Mean SBP (mm Hg)	155.85	113.00
	Mean DBP (mm Hg)	101.92	74.12
8.	Uric Acid (mg / dl)	3.0 – 8.2	3.0 – 7.2
9.	Mean Uric Acid	5.71	3.87

Analysis of Cases and Controls in Relation to Age

The age of the subjects in both groups ranges from 20 – 50 yrs. The mean and standard deviation for age of the cases and controls are 37.34 ± 2.7 and 37.21 ± 2.6 respectively, there is no significant difference among the cases and controls with reference to the age (p = 0.35, not significant).

Table - 3

Cases and Controls in relation to age

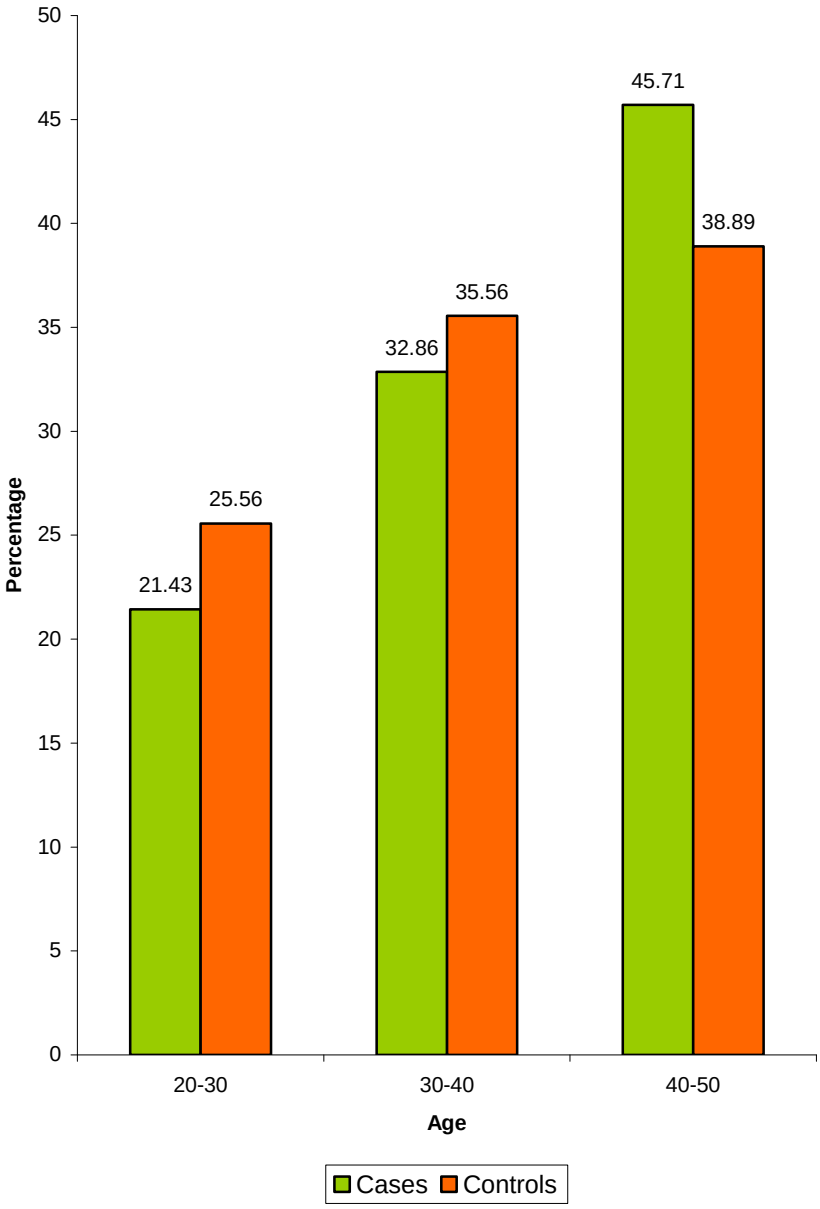
Age Group	Cases*		Controls	
	No.	**%**	**No.**	**%**
20-30	15	21.43	23	25.56
30-40	23	32.86	32	35.56
40-50	32	45.71	35	38.89
Mean	***37.3429***		***37.2111***	
S.D.	***2.67243***		***2.59927***	

** P = 0.353 (not significant)*

Both the study and control groups are comparable with regard to age distribution as evidenced by the following bar diagram.

Fig. 1

Cases and Controls in relation to age



Analysis of Cases and Controls with regard to Sex Distribution

In 70 cases the subjects involved in this study are 43 males and 27 females. In 90 controls, there are 52 males and 38 females.

Table - 4

Cases and Controls in relation to gender

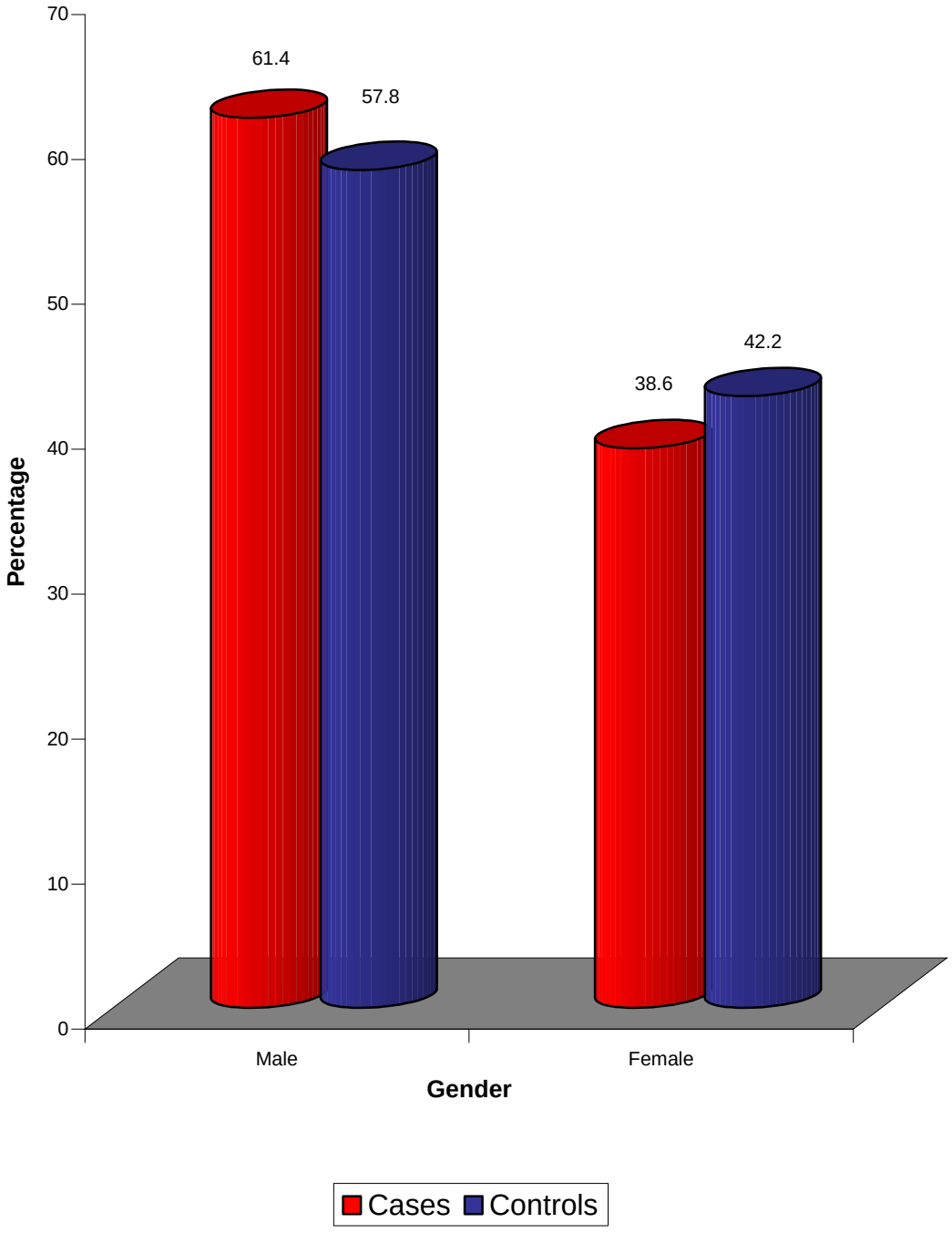
Sex	Cases*		Controls	
	No.	%	No.	%
Male	43	61.4	52	57.8
Female	27	38.6	38	42.2

** P = 0.240 (Not significant)*

The Sex distribution of the study group and control group does not differ.

Fig. 2

Cases and Controls in relation to gender



Analysis of cases and controls in relation to BMI

The study subjects whose BMI > 30 are excluded from the study as BMI >30 has a strong association with hyperuricemia.

The mean and standard deviation of BMI for the cases and controls are 25.06 ± 2.5 and 24.99 ± 2.88 respectively. The details are shown in Table 5 given below.

There is no significant difference among cases and controls with regard to BMI.

Table - 5

Cases and Controls with respect to BMI

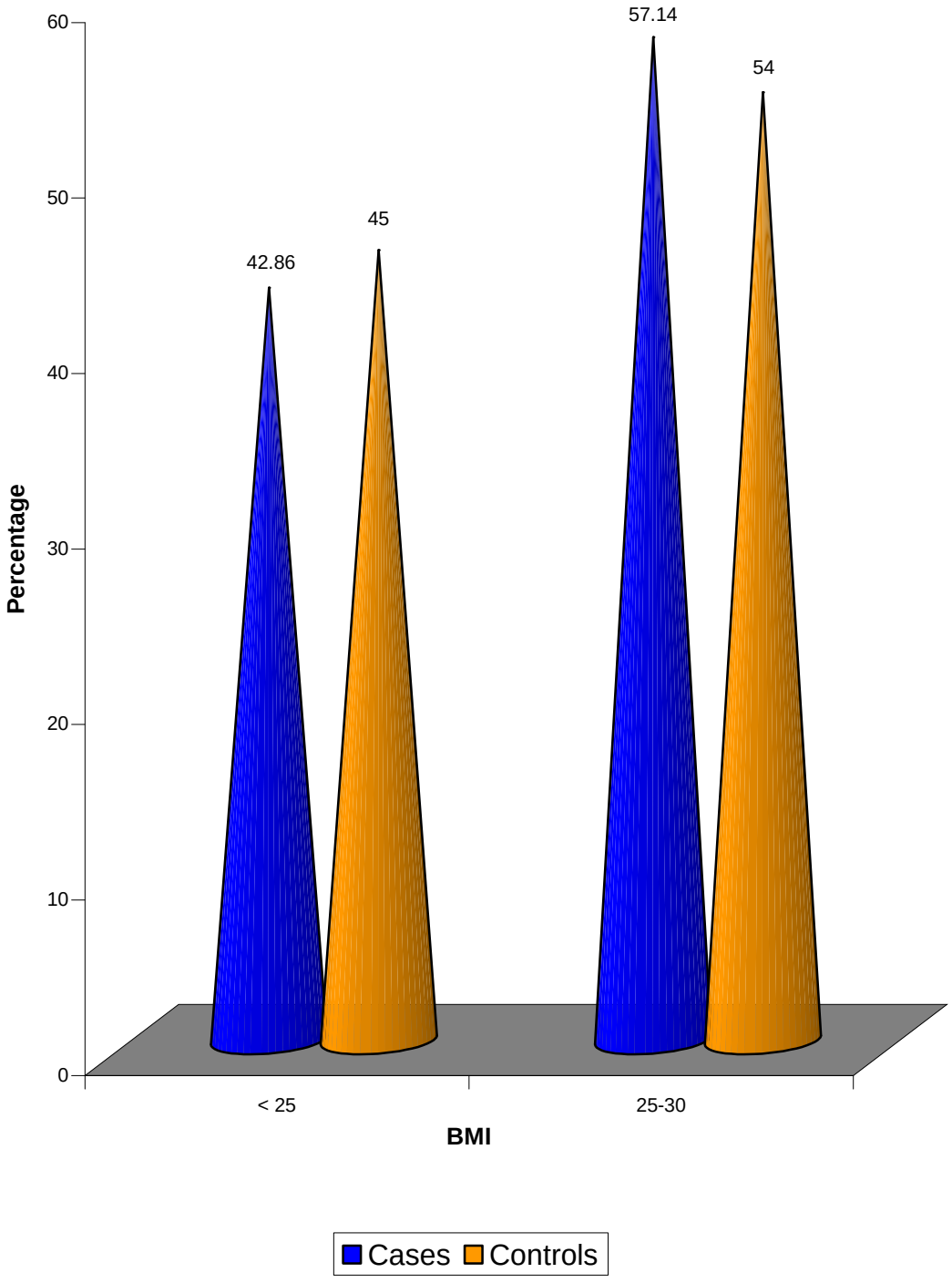
BMI	**Cases***		**Controls**	
	No.	**%**	**No.**	**%**
< 25	30	42.86	41	45
25-30	40	57.14	49	54
Mean	***25.07***		***24.99***	
S.D.	***2.56***		***2.88***	

** P = 0.205 (Not Significant)*

The following bar diagram shows both the study and control groups are comparable with regard to BMI.

Fig. 3

Cases and Controls with respect to BMI



Distribution of cases and controls in relation to selected cardiovascular risk factors

Table - 6

Cases and Controls in relation to Selected Cardiovascular Risk Factor - Smoking (Males)

Smoking	Cases*		Controls	
	No.	%	No.	%
Yes	26	60.47	30	57.69
No	17	39.53	22	42.31
Total	***43***	***100***	***52***	***100***

P = 0.655 (Not Significant)

Table – 7

Selected Cardiovascular Risk Factor – Family History

Family History	Cases*		Controls	
	No.	%	No.	%
Yes	40	57.1	49	54.4
No	30	42.9	41	46.6

P = 0.404 (Not Significant)

Both the groups are comparable with regard to selected cardiovascular risk factors.

Fig. 4

Cases and Controls in relation to Smoking (Males)

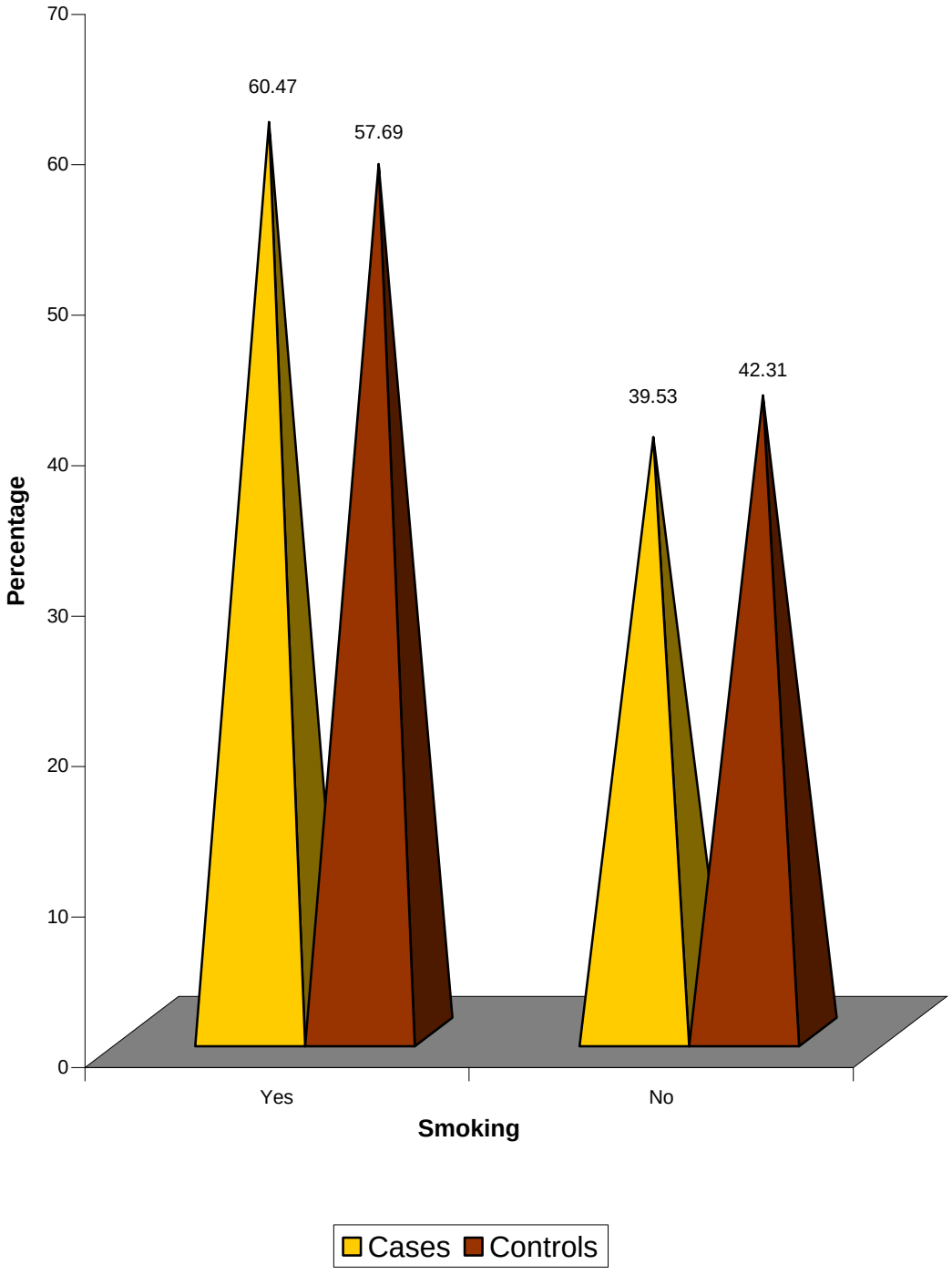
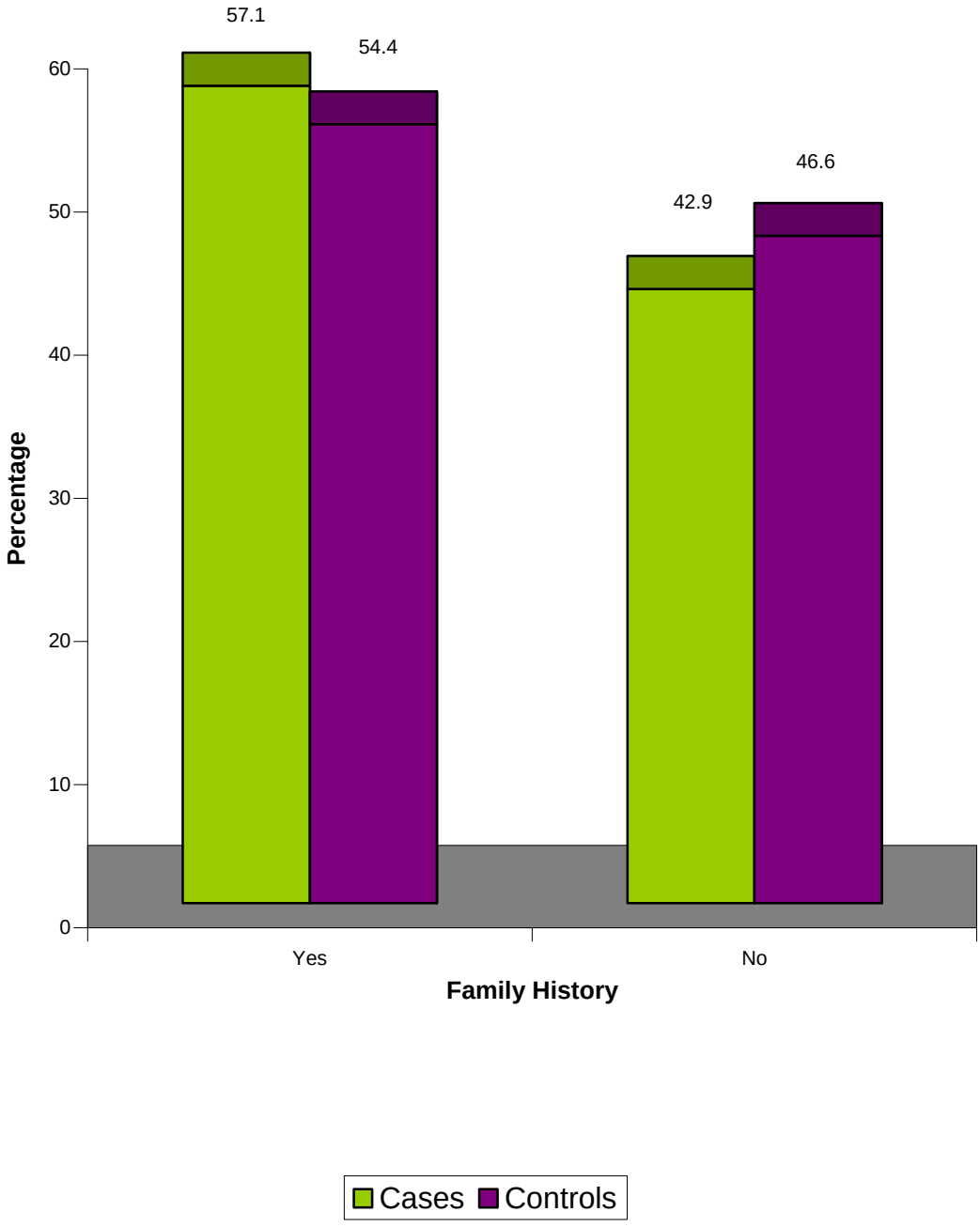


Fig. 5

Cases and controls in relation to Family History



Distribution of blood pressure in cases and controls

The mean and standard deviation of systolic blood pressure in cases and controls are 155 ± 12.7 and 113.00 ± 7.41 respectively.

Similarly, the mean and standard deviation of diastolic blood pressure in cases and controls are 101 ± 17.35 and 74 ± 8.39 respectively.

Table - 8

Cases and Controls in relation to Blood Pressure

Blood Pressure	Cases*		Controls	
	Mean	S.D.	Mean	S.D.
Systolic	155	12.73	113	7.41
Diastolic	101	17.35	74	8.39

Analysis of Serum Uric Acid in study and control groups

Serum uric acid in the study population and control varied from 3.0 to 8.2 mg/dl and 3.0 to 7.2 mg/dl respectively. The mean and standard deviation of uric acid among cases is 5.71 ± 1.06, while in control it is 3.87 ± 0.84 respectively.

The details are given in the table 9 and table 10 below.

Table – 9

Serum Uric Acid in Cases and Controls

Serum Uric Acid	Cases		Controls	
	Mean	**S.D.**	**Mean**	**S.D.**
	5.71	1.07	3.87	0.84

P = 0.021 (Significant)

Table - 10

Hyper Uricemia in Cases and Controls

Hyper Uricemia	Cases				Controls			
	No.	**%**	**Mean**	**SD**	**No.**	**%**	**Mean**	**SD**
Present	21	30.0	6.98	0.69	04	04.4	7.12	0.39
Absent	49	70.0	5.18	0.70	86	95.6	3.72	0.50

P = 0.021 (Significant)

Fig. 6

Cases and Controls in relation to Uric Acid

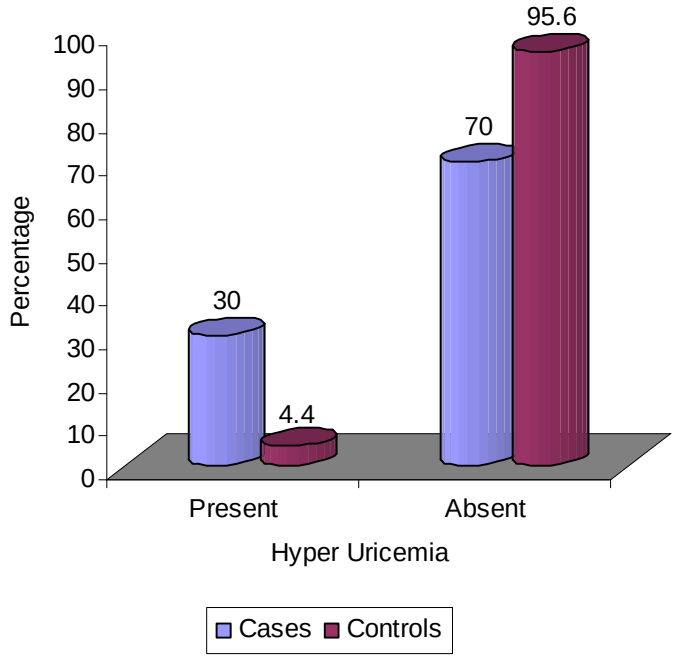
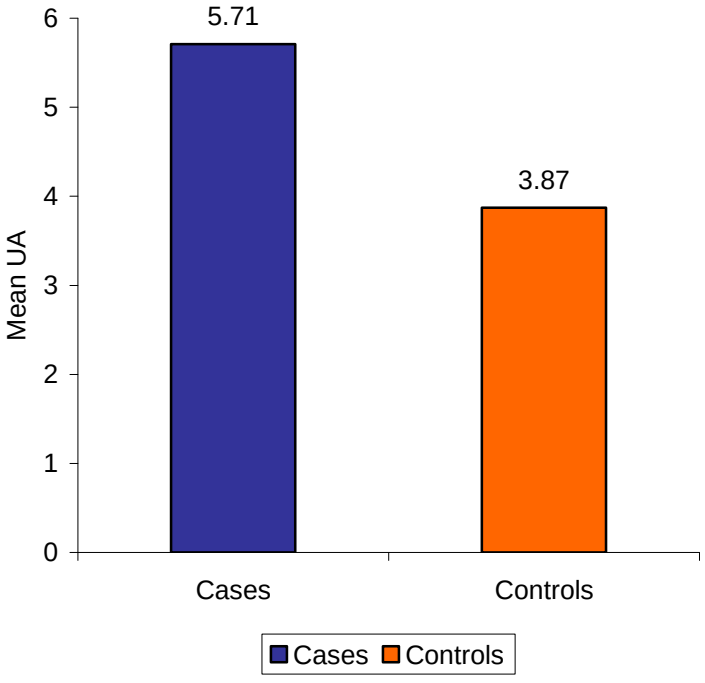


Fig. 7

Mean Uric Acid Level in Cases and Controls



Analysis of Gender Distribution of cases with regard to Serum Uric Acid

The mean of serum uric acid in males is 6.12 ± 0.5 and 5.5 ± 0.7 in females. The details are shown in the following Table 11.

Table – 11

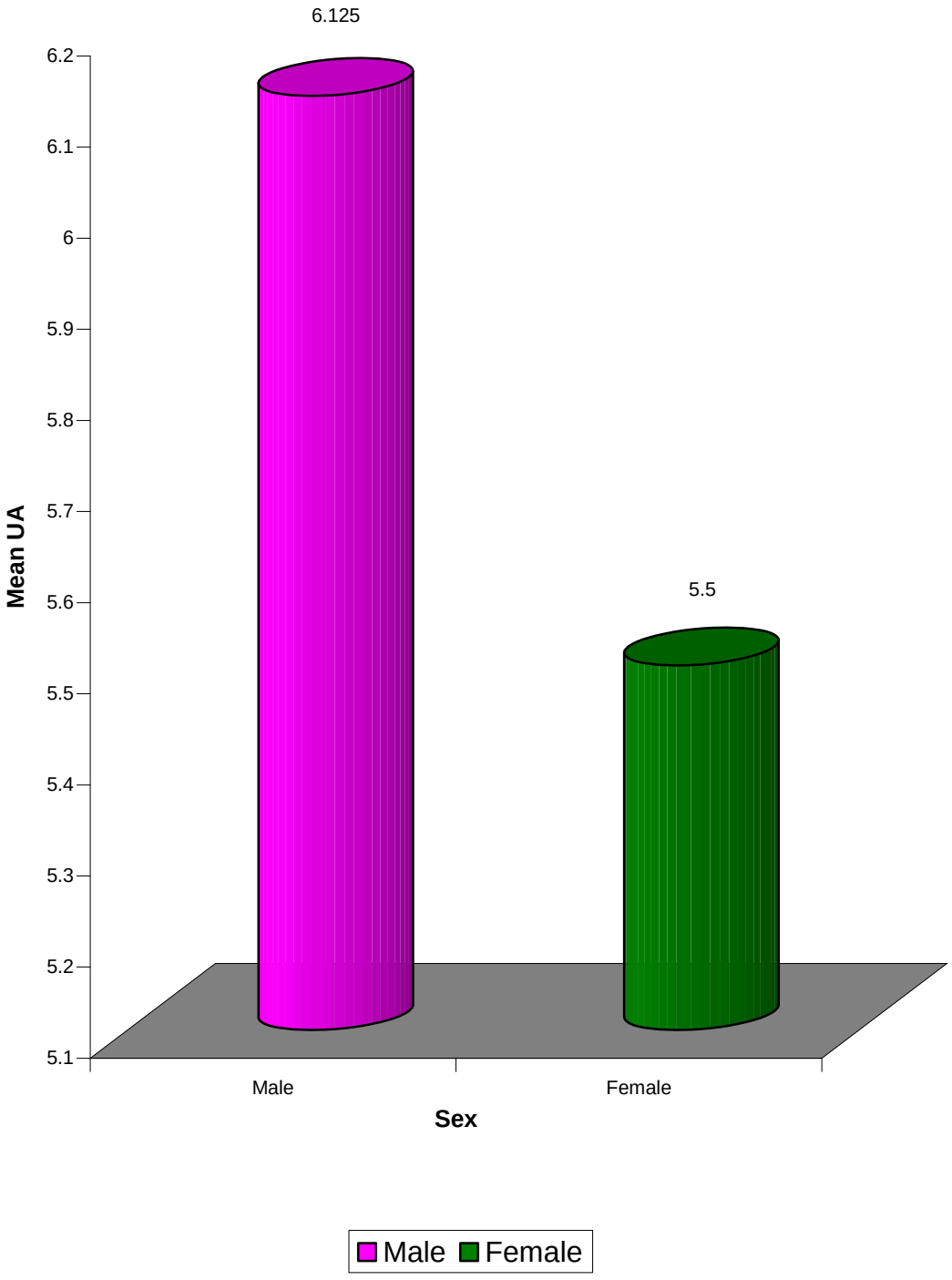
Serum Uric Acid values in relation to gender among cases

Sex	Cases			
	No.	Mean	SD	P
Male	43	6.12	0.49	0.0309 Significant
Female	27	5.50	0.70	

From this study mean uric acid levels is higher in males than females and the statistical difference is significant.

Fig. 8

Serum Uric Acid values in relation to gender among cases



Serum Uric Acid in relation to BMI in cases

The mean and standard deviation of serum uric acid in study subjects whose BMI < 25 is 5.50 ± 0.99 and in whose BMI > 25 is 5.86 ± 1.1. The statistical difference found is not significant between the two groups as the p value = 0.362 (Not significant).

The details are shown in Table 12 given below.

Table – 12

Uric acid in relation to BMI in cases

BMI	Number	Mean of Uric Acid	S.D.
< 25	30	5.50	0.99
> 25	40	5.86	1.10

P = 0.362 (Not Significant)

The study shows the uric acid level between two groups (BMI < 25 and > 25) does not differ. But Nakanishi et al. showed that hyperuricemia is more correlated with low BMI subjects than high BMI subjects in hypertension.

Analysis of uric acid in relation to waist circumference abnormality

Table – 13

Waist abnormality and hyper uricemia in cases

Waist Abnormality (Males > 102 cm; Females > 88 cm)	Number	Mean of Uric Acid	S.D.
+	9	5.8889	0.75572
-	61	5.6836	1.10773

P = 0.578 (Not Significant)

Waist circumference is a reliable marker for central obesity. Waist abnormality is said to be present in males if it is more than 102 cm, and in females more than 88 cm.

The mean and standard deviation of uric acid in cases with waist abnormality is 5.88 ± 0.75 and in subjects without waist abnormality is 5.68 ± 1.1. There is no significant difference between the two groups.

Analysis of Uric acid in relation to smoking (males)

The mean & standard deviation of uric acid in cases with history of smoking is 5.3 ± 1.14. Similarly the mean and standard deviation in cases without history of smoking is 6.27 ± 1.17. There is no significant difference between the two groups with regard to uric acid as the P value is 0.56.

Table – 14

Smoking and Uric acid in cases

Smoking	Number	Mean of Uric Acid	S.D.
+	26	5.38	1.14
-	17	6.27	1.17

P = 0.56 (Not Significant)

Analysis of Uric acid and metabolic syndrome

Out of 100 cases 30 subjects were found to have metabolic syndrome. Similarly, out of 100 controls 10 subjects were found to have the syndrome. The mean & standard deviation of uric acid in cases with metabolic syndrome is 6.13 ± 0.91 and in controls it is 3.68 ± 0.94.

The statistical test shows a significant difference between the two groups with regard to metabolic syndrome. (P value = 0.039) as also evidenced by other studies. The details are given in the following table no.15.

Table – 15

Uric acid and metabolic syndrome

Metabolic syndrome	Cases				Controls			
	No.	%	Mean	SD	No.	%	Mean	SD
Present	08	27	6.13	0.91	01	10	3.68	0.94
Absent	22	73			09	90		

P = 0.039 (Significant)

DISCUSSION

CHAPTER - VI

DISCUSSION

In this study, the relation of serum uric acid to BP in new and recent onset hypertensive adults without any target end organ damage was examined. The study was based on strong epidemiologic data that have linked serum uric acid to hypertension in humans[18,19,22-29] and experimental animal data, which suggest that hyperuricemia contributes to hypertension.[31,32]

The experimental studies further demonstrated that hyperuricemia caused preglomerular vascular disease via a BP-independent pathway [31], and once vascular changes were established, the hypertension was driven by the kidney, and lowering uric acid levels was no longer protective.[31] It is therefore hypothesized that if serum uric acid were important in the genesis of primary hypertension, then the relation would be greatest in the new and recent onset hypertensive subjects.

To test this hypothesis, 70 adults of which 43 males and 27 females referred for hypertension were evaluated. Both the cases and controls selected were matched for age, sex and BMI. The subjects in our sample included both young and old (20 to 50 years), but most of the studies included only younger subjects. Because Nakanishi et al.[28] found a

strong association among those with lower BMI, a possible relationship between UA and BMI (< 25 and > 25 kg/m^2) was also examined.

The mean age of the study population was 37.3 and 37.2 in both cases and controls respectively.

Blood pressure in both controls and cases were measured according to JNC VII classification and the mean blood pressure in cases was 155 / 101 and in controls it was 113 / 74 respectively.

Uric acid was normally distributed among both subjects and was examined as a continuous variable. The mean plasma uric acid in cases was 5.7 mg/dl ± 1.0 (range 3.0 to 8.2) and the mean plasma uric acid in controls was 3.8 mg/dl ± 0.8 (range 3.0 to 7.2). The association between uric acid and hypertension was analyzed using student 't' test and statistical difference was assessed by Pearson coefficient.

The study showed a significant difference between the hypertensive subjects and the normotensive controls (p value = 0.021).

If uric acid was simply a marker, then a similar degree of hyperuricemia in the control subjects would be expected, and this was not observed.

Though mean uric acid was higher is subjects with BMI ≥ 25 (5.86) than those subjects with BMI < 25 (5.50) the relationship between

uric acid and BMI did not show a statistical difference in this study, but Nakanishi et al. found a stronger association among those with lower BMI.

Males were found to be more hyperuricemic than females in the study in which the difference is significant ($p = 0.03$).

Many studies have showed that hyperuricemia is closely associated with waist abnormality. The study revealed that there was not a significant difference between waist abnormality and uric acid in cases ($p = 0.57$).

The study also examined a possible relationship between smoking and hyperuricemia in hypertensive individuals. It was to observe that whether smoking influences hyperuricemia in hypertension.

The study showed that there is no significant difference between smoking (present or absent) and hyperuricemia ($P = 0.56$).

The study also examined a relation between metabolic syndrome and uric acid. Uric acid is associated with metabolic syndrome as indicated by various studies. It was also observed that a significant difference was obtained by the test between the two groups ($P = 0.039$). It is also to be noted that the sample size in both groups were small.

There is a future perspective that hypertension can be treated by lowering uric acid levels particularly in new and recent onset

hypertension. Once microvascular lesion develops, lowering uric acid levels will not be useful, as the late stage hypertension is uric acid independent and salt sensitive.

One study showed [48] lowering uric acid levels in adolescent hypertension resulted in BP reduction. The results represent a new potential therapeutic approach, although not a fully developed therapeutic strategy due to potential adverse effects. These preliminary findings require confirmation in larger clinical trials.

CONCLUSION

CHAPTER - VII

CONCLUSION

- Serum uric acid is strongly associated with BP in new and recent onset primary hypertension.
- An elevated or high–normal serum uric acid value>5.5mg/dl[19,20,24] (mean uric acid-5.7 in this study) in an adult being evaluated for hypertension strongly supports the presence of primary hypertension. The remarkable association of uric acid with BP in adults is consistent with recent animal model data and the hypothesis that uric acid might have a pathogenic role in the development of hypertension.
- Males have a higher degree of hyperuricemia than females in hypertensive patients.
- Though mean uric acid is higher in study subjects whose BMI > 25 than those subjects with BMI < 25, the association is not significant.
- There is no stronger association of hyperuricemia in hypertension patients with regard to waist abnormality.

- There is no significant difference among hypertensive males with regard to uric acid and smoking. Smoking does not show an influence on hyperuricemia in cases.
- Hyperuricemia is associated with metabolic syndrome, as evidenced by other studies.

BIBLIOGRAPHY

CHAPTER - VIII

BIBLIOGRAPHY

1. Chobanian A, Bakris G, Black H, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee. JAMA 289: 2560-2572, 2003.
2. Daniel Fieg, Duk – Hee Kang – Uric Acid and Cardiovascular risk – NEJM 2008.
3. Wu X, Muzny DM, Lee CC, Caskey CT. Two independent mutational events in the loss of urate oxidase during hominoid evolution. J. Mo Evol. 1992; 34 : 78 – 84.
4. Selby JV, Friedman GD, Quesenberry CP. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. Am J Epidemiol. 1990; 131:1017 – 1027.
5. Jossa F, Farianro E, Panico S, Krogh V, Celentano E, Galasso R, Mancini M, Trevisan M. Serum uric acid and hypertension : the Olivetti heart study. J. Hum Hypertens. 1994; 8 : 677 – 681.

6. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. N Engl. J. Med. 1966; 275:457 – 464.
7. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension. 1999; 34: 144 – 150.
8. Vaccarino V, Krumholz HM. Risk factors for cardiovascular disease: one down, many more to evaluate. Ann Intern Med. 1999; 131: 62 – 63.
9. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: the NHANES I Epidemiologic Follow – up study. 1971 – 1992. JAMA. 2000; 283:2404 – 2410.
10. Theodore A. Kotchen – Harrison's principles of Internal medicine – 17th Edition.
11. Robert L. Wortmann – Harrison's Principles of Internal Medicine – 17th Edition.
12. U.R.K. Rao – API-Textbook of Medicine – 8th Edition.
13. Mohamed FA: On chronic Bright's disease, and its essential symptoms. Lancet 1: 399-401, 1879.
14. Haig A: On uric acid and arterial tension. BMJ1: 288-291, 1889.
15. Huchard H: Arteriolosclerosis: Including its cardiac form. JAMA 53: 1129-1132, 1909.

16. Gertler MM, Garn SM, Levine SA: Serum uric acid in relation to age and physique in health and in coronary heart disease. Ann Intern Med 34: 1421-1431, 1951.

17. Breckenrige A: Hypertension and hyperuricemia, Lancet 1: 15-18, 1966.

18. Brand FN, McGee DL, Kannel WB, Stokes J 3rd, Castelli WP: Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol 121: 11-18, 1985.

19. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH: Hyperuricemia in primary and renal hypertension. N Engl J Med 275: 457-464, 1966.

20. Kinesey D, Walther R, Sise HS, Whitelaw G, Smithwick R: Incidence of hyperuricemia in 400 hypertensive subjects. Circulation 24: 972-973, 1961.

21. Curtis JJ, Luke RG, Jones P, Diethelm AG: Hypertension in cyclosporine – treated renal transplant recipients is sodium dependent. Am J Med 85: 134-138, 1988.

22. Johnson RJ, Rodrigyuez-Iturbe B, Schreiner GF, Herrera-Acosta J: Hypertension: A microvascular and tubulointerstitial disease. J Hypertens 20 [Supp 1 3] : S1-S7, 2002.

23. Pearson T, Blair S, Daniels S, Eckel RJ, Fair FM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Miller NH, Lauer RM, Ockene IS, Sacco RL, Sallis JF Jr, Smith SC Jr, Stone NJ, Taubert KA: AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 106: 388-391, 2002.

24. Feig DI, Johnson RJ: Hyperuricemia in childhood primary hypertension, Hypertensions 42: 247-252, 2003.

25. Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, Mancini M, Trevisan M: Serum uric acid and hypertension: The Olivetti heart study. J Hum hypertens 8 : 677-681, 1994 [Medline].

26. Friedman GD, Quesenberry CP Jr: Precursors of essential hypertension: Pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. Am J Epidemiol 131: 1017-1027, 1990.

27. Kahn HA, Medalie JH, Neufeld HN, Riss E, Goldbourt U: The incidence of hypertension and associated factors: The Israel ischemic heart study. Am Heart J 84: 171-182, 1972.

28. Nakanishi N, Okamato M, Yoshida H, Matsuo Y, Suzuki K, Tatara K: Serum uric acid and the risk for development of hypertension and impaired fasting glucose or type II diabetes in Japanese male office workers. Eur J Epidemiol 18: 523-530, 2003.

29. Hunt SC, Stephenson SH, Hopkins PN, Williams RR: Predictors of an increased risk of future hypertension in Utah. A screening analysis. Hypertension 17:969-976, 1991.

30. Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML: Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. Hypertension 42: 474-480, 2003.

31. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension. 38: 1101-1106, 2001.

32. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, Lan HY, Johnson RJ: Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism, Am J Physiol Renal Physiol 282: F991-F997, 2002.

33. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truoung L, Harris R, Johnson RJ: A role for uric acid in the progression of renal disease. J Am Soc Nephrol 13: 2888-2897, 2002.

34. Price K, Mu W, Raines E, Nakagawa T, Johnson RJ: Expression of a urate transporter in human vascular smooth muscle cells. J Am Soc Nephrol 14: 145A, 2003.

35. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, Mazzali M, Johnson RJ: Uric acid hominoid evolution and the pathogenesis of salt-sensitivity. Hypertension 40: 355-360, 2002

36. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikth-Hamad D, Lan HY, Feng L, Johnson RJ: Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 41: 1287-1293, 2003.

37. Kang DH, Joly AH, oh SW, Hugo C, Kerjaschki D, Gordon KL, Mazzali M, Jefferson JA, Hughes J, Madsen KM, Schreiner GF, Johnson RJ: Impaired angiogenesis in the remnant kidney model: I. Potential role of vascular endothelial growth factor and thrombospondin-1. J Am Soc Nephrol 12: 1434-1447, 2001.

38. Kang DH, Hughes J, Mazzali M, Schreiner GF, Johnson RJ: Impaired angiogenesis in the remnant kidney model: II. Vascular endothelial growth factor administration reduces renal fibrosis and stabilizes renal function. J Am Soc Nephrol 12:1448-1457, 2001.

39. Kang DH, Kim YG, Andoh TF, Gordon KL, Suga S, Mazzali M, Jefferson JA, Hughes J, Bennett W, Schreiner GF, Johnson RJ: Post-cyclosporine-mediated hypertension and nephropathy: Amelioration by vascular endothelial growth factor. Am J Physiol renal Physical 280: F727-F736, 2001.

40. Neal D, Tom B, Gimson A, Gibbs P, Alexander GJ: Hyperuricemia, gout and renal function after liver transplantation. Transplantation 72: 1689-1691, 2001.

41. Klein R, Klein BE, Cornoni JC, Maready J, Cassel JC, Tyroler HA: Serum uric acid. Its relationship to coronary heart disease risk factors and cardiovascular disease, Evans Country, Georgia. Arch Intern Med 132:401-410, 1973.

42. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K: Serum uric acid and the risk for hypertension and type 2 diabetes in Japanese men. The Osaka Health Survey. J Hypertens 19:1209-1215, 2001.

43. Alper A, Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL: Childhood uric acid predicts adult blood pressure. Hypertension 45: 34-48, 2005.

44. Sundstrom J, Sullivan L, D'Agostino R, Levy D, Kannel WB, Vasan RS: Relationship of serum uric acid to longitudinal blood pressure tracking and hypertension incidence in the Framingham Heart Study. Hypertension 45:28-33, 2005.

45. Rovda Iu I, Kazakova LM, Plaksina EA: [Parameters of uric acid metabolism in healthy children and in patients with arterial hypertension]. Pediatriia 19-22, 1990.

46. Torok E, Gyarfas I, Csukas M: Factors associated with stable high blood pressure in adolescents. J Hypertens Suppl 3:S389-S390, 1985.

47. Gruskin AB: The adolescent with essential hypertension, Am J Kidney Dis 6:86-90, 1985.

48. Daniel Feig, Beth Solestsky–JAMA, 2008. Allopurinol on Blood Pressure of Adolescents with newly diagnosed essential hypertension.

49. Nagahama K, Inove T, Iseki K, Touma T, Kinjo K, Ohya Y, Takashito S: Hyperuricemia as a predictor of hypertension in a screened cohort in Okinawa, Japan. Hypertens Res 27: 835-841, 2004.

50. Feig DI, Nagakawa T, Karumanchi SA et al. Uric acid nephron number and the pathogenesis of essential hypertension, kidney Int 2004; 66: 281-7.

PROFORMA

CHAPTER – IX

ANNEXURE

A STUDY ON THE ASSOCIATION OF SERUM URIC ACID IN NEW & RECENT ONSET PRIMARY HYPERTENSION

PROFORMA

NAME: AGE: SEX: O.P.NO:

OCCUPATION: ADDRESS:

HISTORY: - Headache - Breathlessness

- Giddiness - Palpitation

- Chest pain - Edema legs

PAST HISTORY:

1) HT-YES/NO DURATION: Rx DETAILS:

2) DM-YES/NO DURATION: Rx DETAILS:

3) CKD-YES/NO DURATION: Rx DETAILS:

4) CCF-YES/NO DURATION: Rx DETAILS:

DRUG HISTORY: YES/NO CVA - YES/NO GOUT-YES/NO

CAD-YES/NO MALIGNANCY: YES/NO

SKIN DISORDERS: YES/NO THYROID DISORDER-YES/NO

PERSONAL HISTORY:

DIET: SALT RESTRICTED: YES/NO

SMOKING: YES/NO ALCOHOL: YES/NO TOBACCO: YES/NO

FAMILY HISTORY:

GENERAL EXAMINATION:

HT: WT: BMI: WAIST:

ANAEMIA

CYANOSIS

CLUBBING

PEDAL EDEMA

ICTERUS

GENERALISED LYMPHADENOPATHY

THYROID

VITALS: PR

BP - LEFT ARM RIGHT ARM

1.

2.

MEAN:

Higher of the mean:

SYSTEMIC EXAMINATION:

CVS:

RS:

ABD:

CNS:

FUNDUS EXAMINATION:

INVESTIGATIONS:

1.	COMPLETE HAEMOGRAM	-	
2.	URINE-ALBUMIN	-	
	SUGAR	-	
	DEPOSITS	-	
3.	FASTING BLOOD SUGAR	-	
4.	BLOOD UREA	-	
5.	SERUM CREATININE	-	
6.	SERUM URIC ACID	-	
7.	LIPID PROFILE	-	TOTAL CHOLESTROL TRIGLYCERIDES HDL LDL VLDL
8.	LIVER FUNCTION	-	SERUM BILIRUBIN TRANSAMINASES, ALKALINE PHOSPHATASE, SERUM ALBUMIN AND GLOBULIN
9.	THYROID FUNCTION TESTS	-	T3, T4, TSH
10.	ECG	-	

MASTER CHART

CASES

S.No	Name	Age	Sex	Op.No	Ht	Wt	BMI	Waist	BP	Smoking	Family History	Urea	Sugar	Creatinine	Cholestrol	TGL	HDL	Metabolic syndrome	UA	xx
1	Rajendran	45	1	2808	168	62	21.97	100	170/100	1	1	24	9.8	0.6	181	178	42	2	5.4	2
2	Pushpa	35	2	63000	155	69	28.72	87	160/100	-	1	29	109	0.8	180	165	52	2	7.5	2
3	Rajendran	48	1	82458	169	72	25.21	99	150/80	2	1	33	90	0.8	203	168	45	2	4.7	2
4	Ravi	41	1	517	165	60	22.04	98	160/90	1	1	30	98	0.7	210	240	38	1	5.7	2
5	Vetrivel	30	1	2807	170	65	22.49	94	160/90	1	1	25	95	0.7	180	40	42	2	6	2
6	Mahabunisha	36	2	4738	152	62	26.84	86	140/96	-	1	26	101	4.8	158	195	38	1	4.1	2
7	B.K. Balu	33	1	5959	159	70	27.69	100	180/106	2	1	26	98	0.5	48	138	41	2	8.2	2
8	Ahamed	43	1	1939	172	68	22.99	99	150/100	1	1	24	110	0.7	161	210	47	1	4.5	2
9	Maheswari	45	2	2875	159	60	23.73	90	150/92	-	2	25	96	0.6	183	191	45	2	5.2	2
10	Kalaiselvan	38	1	377	172	64	21.63	106	150/90	1	1	22	85	0.8	162	140	37	1	4	2
11	Murugan	24	1	4192	169	75	26.26	96	160/90	2	1	22	98	0.7	98	210	42	2	7.7	2
12	Palani	45	1	425	172	75	25.35	96	150/90	2	2	22	97	0.6	217	16	38	2	5.7	2
13	Ramesh	38	1	508	175	70	22.86	95	140/90	2	1	26	112	0.7	145	204	42	2	4.5	2
14	Maruthamuthu	37	1	615	170	69	23.88	104	150/90	2	1	24	70	96	221	380	35	1	4.2	2
15	Padmavathy	40	2	619	158	70	28.04	90	160/110	-	1	24	85	0.6	216	110	52	2	5.8	2
16	Kannan	36	1	2709	165	70	25.71	96	150/90	1	1	25	91	0.6	110	275	36	2	5.2	2
17	Jesudhass	41	1	1224	170	69	23.88	99	160/90	2	1	25	81	0.8	197	183	38	2	4.6	2
18	Thangaraj	40	1	4538	175	64	21.1	100	160/100	2	1	24	100	0.7	191	220	40	2	6	2
19	Ayeehaseevi	46	1	2086	159	67	26.5	88	150/100	-	2	28	95	0.7	190	190	51	2	6.2	2
20	Thangaponnu	30	2	2539	156	69	28.35	86	140/90	-	2	25	96	0.6	180	143	55	2	5.5	2
21	Jawahar	23	1	2619	174	79	26.09	92	150/90	-	1	25	96	0.6	183	191	46	2	5.2	2
22	Duraisamy	42	1	624	169	63	22.06	98	160/90	1	1	26	93	0.8	165	220	48	2	4.8	2
23	Mongajee	42	2	2778	152	55	23.81	84	150/90	-	2	30	119	0.8	210	165	51	2	3.8	2
24	Balan	28	1	78560	170	75	25.95	96	150/90	-	1	18	108	0.5	188	147	42	2	5.4	2
25	Giridaran	45	1	84335	173	79	26.4	95	130/90	2	1	30	107	0.8	180	132	45	2	7.6	2
26	Fathima	45	2	2036	159	70	27.69	87	160/90	-	1	25	104	0.6	245	217	47	2	6.1	2
27	Kannagi	45	2	2912	159	70	27.69	94	150/90	-	1	23	117	0.5	213	160	49	1	4	2
28	Selvi	33	2	2038	158	75	30.00	86	180/90	-	2	18	90	0.5	209	160	46	2	7	2
29	Alagan	47	1	55070	169	74	25.91	105	150/90	2	2	37	88	0.8	172	115	38	1	5.4	2
30	Rajaram	43	1	2909	174	68	22.46	97	170/100	2	2	40	80	0.8	153	131	46	2	7.2	2
31	Karupayya	35	1	87112	172	70	23.66	105	150/90	2	2	27	113	0.8	150	146	45	1	4.6	2
32	Pandiyan	45	1	2884	173	67	22.39	96	160/90	2	2	40	92	1.2	193	165	42	2	5.9	2

33	Katharnath	50	1	99	170	72	24.91	98	170/90	1	2	27	105	0.6	211	218	43	2	6	2
34	Solaimuthu	43	1	2981	174	69	22.79	92	150/90	1	1	42	79	1	203	181	42	2	5	2
35	Chellamuthu	28	1	2833	170	71	24.57	95	170/90	2	1	20	91	0.6	206	198	44	2	5	2
36	Pappa	38	2	74466	156	72	29.59	95	170/100	-	1	18	82	0.6	241	181	45	1	7	2
37	Muthumani	44	2	2488	159	70	27.69	90	160/90	-	1	20	105	0.6	160	146	42	1	6.6	2
38	Muhamed Umar	37	1	94487	170	75	25.95	97	140/90	1	2	21	90	0.6	166	102	46	2	3.2	2
39	Rani	46	2	994	162	67	25.53	88	180/90	-	1	22	77	0.5	296	194	45	2	4	2
40	Usharani	40	2	2136	159	62	24.52	92	140/90	-	2	21	95	0.5	266	161	48	1	3	2
41	Thulasimmal	38	2	4057	160	74	28.91	95	170/90	-	1	36	90	1.1	188	126	52	2	6.1	2
42	Maniyarose	29	2	1083	162	55	20.96	82	140/90	-	2	26	91	0.7	251	148	50	2	3	2
43	Usha	42	2	2104	155	70	29.14	89	160/90	-	1	21	98	0.5	138	145	51	2	5.8	2
44	Susila	45	2	3502	153	62	26.49	92	170/90	-	1	24	96	0.5	194	145	52	2	6.1	2
45	Dhanalakshmi	35	2	1438	158	72	28.84	100	150/90	-	2	22	102	0.7	187	143	47	1	5	2
46	Chinnaponnu	49	2	81295	157	62	25.15	85	170/90	-	1	40	88	0.9	254	148	48	2	6.3	2
47	Durairaj	40	1	113	174	74	24.44	96	140/90	1	2	37	82	0.6	168	159	38	1	4.2	2
48	Venkatachalam	45	1	571	170	70	21.55	106	150/90	1	1	40	91	0.6	138	190	42	1	4.5	2
49	Raji	50	2	2629	169	78	27.31	94	160/90	-	1	32	83	0.5	257	193	40	1	5	2
50	Chellakannu	35	2	1501	157	60	24.34	86	150/90	-	2	22	105	0.5	245	193	48	1	4	2
51	Maheswari	37	2	5785	152	61	26.4	84	150/90	-	1	29	85	0.6	146	132	52	2	4.7	2
52	Perumal	50	1	269	174	79	26.09	100	160/90	1	1	3.7	91	0.6	248	182	45	2	5.5	2
53	Ponnu	50	2	4725	160	64	25	95	150/90	-	2	35	81	0.7	222	190	48	1	4.5	2
54	Sivakumar	45	1	2080	177	78	24.9	96	160/90	1	1	32	100	0.6	189	143	45	1	5.2	2
55	Ramamoorthi	48	1	364	172	70	23.66	100	170/100	1	2	25	98	0.8	137	140	42	1	7.1	2
56	Rabia	48	2	1419	160	71	27.73	87	150/90	-	1	35	109	0.5	190	132	52	1	4.7	2
57	Jaled	30	1	1980	175	77	25.14	102	150/90	1	2	32	103	0.9	240	152	45	2	4.1	2
58	Ravichandran	50	1	2800	170	80	27.68	104	170/100	2	2	39	75	0.8	183	140	42	2	7.7	2
59	Shahiva Banu	33	2	508	152	58	25.1	86	150/90	-	2	22	82	0.7	285	193	52	2	4.9	2
60	Malliga	30	2	193	155	62	25.81	88	150/100	-	2	37	73	0.7	270	143	50	2	5	2
61	Ayeesha	30	2	4198	156	70	28.76	89	150/90	-	1	29	109	0.6	263	139	49	1	4.3	2
62	Rani	25	2	2793	158	60	24.03	86	170/90		1	25	96	0.5	189	146	48	2	6.1	1
63	Rangan	37	1	5192	174	78	25.76	100	150/90	1	1	24	98	0.7	214	167	42	2	5.5	2
64	Muthu	26	1	2619	170	74	25.61	102	160/90	1	1	20	80	0.5	180	132	48	2	7.1	1
65	Saravanan	33	1	4312	176	71	22.92	97	150/90	1	2	27	89	0.7	192	172	42	2	4.5	2
66	Raju	29	1	2819	169	68	23.81	100	170/90	2	2	23	106	0.5	224	182	40	1	7.5	1
67	Gurunathan	42	1	719	175	76	24.82	95	150/90	1	1	29	90	0.7	256	192	42	2	5.1	2
68	Samikannan	49	1	183	165	75	27.55	105	140/90	1	1	32	82	0.5	212	148	45	2	5.6	2

69	Samuel	32	1	2419	174	76	25.1	92	160/90	1	2	22	76	0.9	175	132	42	2	7.3	1
70	Naganathan	40	1	19/31913	170	69	23.88	97	150/90	1	2	28	98	0.6	242	189	40	1	5.5	2
71	Devaraj	37	1	2132	176	72	23.24	98	140/90	1	1	24	86	0.7	189	137	42	2	7.6	1
72	Arun	25	1	2719	172	70	23.66	100	150/100	2	1	29	76	0.5	240	140	45	2	7.2	1
73	Kumarasamy	46	1	983	174	72	23.78	105	140/90	2	2	27	105	0.9	283	176	42	1	5.6	2
74	Beevi	42	2	5918	159	64	25.32	95	150/90	-	1	32	90	0.7	190	163	48	1	5	2
75	Rengasamy	35	1	3319	170	68	23.53	99	160/90	2	1	26	109	0.9	240	141	45	2	6.3	2
76	Mookan	42	1	719	176	75	24.21	100	150/90	1	1	22	90	0.5	210	145	42	1	5.5	2
77	Sanniyasi	50	1	3519	170	78	26.99	105	140/90	1	1	32	110	0.9	239	183	38	2	7.5	1
78	Karupasamy	40	1	919	169	72	25.21	100	150/90	2	1	35	92	0.7	240	160	42	2	6.1	2
79	Selvi	33	2	2519	159	62	24.52	86	150/100	-	2	29	76	0.5	168	139	49	2	5.5	2
80	Shanthi	28	2	2719	162	68	25.91	87	160/90	-	2	32	88	0.8	159	132	45	2	6.3	1
81	Lakshmi	45	2	81875	160	65	25.39	92	150/90	-	1	36	120	0.9	240	168	47	1	4.9	2
82	Roobi	32	2	4143	165	70	25.71	90	160/90	-	1	25	98	0.9	283	145	55	2	5.2	2
83	Susila	39	2	7189	158	68	27.24	95	150/90	-	1	29	90	0.5	185	156	48	1	5.8	2
84	Murugandham	40	1	5155	175	77	25.14	99	160/90	1	1	28	88	0.7	212	148	45	2	5	2
85	Seethakumar	37	1	4193	169	72	25.21	98	150/90	1	2	26	82	0.5	214	135	42	2	4.9	2
86	Selvam	27	1	2219	170	65	22.49	96	150/100	1	1	22	79	0.6	222	148	42	2	5	2
87	Kuppusamy	42	1	719	160	68	26.56	100	140/90	2	2	29	98	0.9	219	135	43	2	6.1	2
88	Elavarasan	25	1	2169	175	80	26.12	98	165/90	1	2	27	90	0.7	187	148	42	2	7.5	1
89	Muthukumari	28	2	1793	162	62	23.62	85	150/150	-	2	22	80	0.6	219	145	41	2	5.2	2
90	Ranganayaki	42	2	5159	159	60	23.73	84	160/90	-	2	28	76	0.5	190	137	49	2	5.5	2
91	Prema	29	2	2719	162	61	23.24	86	160/100	-	2	25	90	0.7	210	148	51	2	6.1	1
92	Rajamani	35	1	71925	170	72	24.91	96	150/90	-	2	30	90	0.7	210	156	42	2	5.1	2
93	Veerapathran	48	1	8181	172	74	25.01	102	160/90	2	2	24	108	0.6	212	173	42	1	7.2	1
94	Raja	28	1	2513	170	75	25.95	94	160/100	2	2	22	90	0.7	180	142	44	2	6.1	2
95	Kanthasamy	40	1	7193	169	72	25.21	100	150/90	1	2	25	110	0.7	253	163	42	1	7.5	1
96	Munjala	33	2	5192	159	72	28.48	98	150/90	-	2	29	98	0.7	168	138	51	2	5.5	2
97	Nithya	29	2	2719	160	65	25.39	85	160/90	-	2	22	80	0.6	190	140	45	2	5.2	2
98	Mookayee	43	2	6193	162	70	26.67	92	160/90	-	2	26	116	0.6	240	162	45	1	6.3	1
99	Parvathi	33	2	5195	163	68	25.59	86	150/90	-	2	32	90	0.7	190	192	50	2	5.1	2
100	Shanthi	38	2	5194	160	71	27.73	94	150/90	-	2	28	98	0.5	252	172	42	1	6.5	1

Smoking : 1 – Yes ; 2 – No Family History : 1 – Yes ; 2 – No Metabolic Syndrome : 1 – Yes ; 2 – No xx : 1 – elevated ; 2 - Normal
Sex : 1 – Males 2 – Females

CONTROLS

S.No	Name	Age/Sex	Op.No	Ht	Wt	BMI	Waist	BP	Smoking	Family History	Urea	Sugar	Creatinine	Cholestrol	TGL	HDL	Metabolic syndrome	UA	
1	Sathish	36/M	95493	175	75	24.49	96	120/70	Yes	Yes	24	98	0.8	164	102	52	No	3.6	No
2	Murugadass	40/M	82843	170	69	23.88	98	120/70	No	Yes	24	91	0.6	180	84	45	No	3.6	No
3	Prabhakaran	39/M	2602	169	75	26.26	89	110/70	Yes	No	24	87	0.6	219	138	50	No	3.8	No
4	Sivam	44/M	66029	170	74	25.61	92	110/70	Yes	Yes	30	94	0.8	178	150	48	No	4	No
5	Sekar	40/M	96461	169	72	25.21	94	110/76	No	No	26	87	0.7	233	153	52	No	3.5	No
6	Moorthy	27/M	96851	175	78	25.47	98	110/82	Yes	Yes	28	102	0.8	127	133	45	No	3.6	No
7	Selvam	31/M	96883	170	72	24.91	90	110/76	No	Yes	28	88	0.8	216	249	48	No	3.7	No
8	Shanmugam	28/M	93274	169	73	25.56	88	120/70	Yes	No	30	113	0.9	178	150	52	No	3.9	No
9	Ahamed	34/M	96935	175	80	26.12	92	110/80	No	Yes	28	119	0.7	236	130	45	No	3.1	No
10	Veeran	35/M	96941	178	70	22.09	96	110/70	No	No	24	91	0.8	242	144	46	No	3.4	No
11	Ravichandran	27/M	96960	170	70	24.22	92	110/70	Yes	No	26	102	0.8	202	146	50	No	3.6	No
12	Ibrahim	37/M	96953	169	72	25.21	90	120/70	Yes	Yes	28	90	0.8	198	146	52	No	3.6	No
13	Bharathi	29/M	83317	174	70	23.12	86	110/70	No	Yes	25	77	0.8	190	148	44	No	3.9	No
14	Velasamy	30/M	97070	170	65	22.49	99	110/70	Yes	No	30	98	0.9	162	149	48	No	3.5	No
15	Raghu	39/M	97052	180	75	23.15	96	110/76	No	Yes	24	100	0.7	138	145	42	No	3.9	No
16	Saravanan	30/M	97093	174	74	24.44	92	110/70	Yes	No	28	95	0.8	148	136	45	No	3.7	No
17	Palanivel	30/M	82714	170	72	24.91	90	170/70	Yes	No	20	94	0.5	200	236	42	No	4	No
18	Sivanathan	35/M	95443	176	76	24.54	88	110/76	Yes	Yes	18	105	0.6	176	94	50	No	3.5	No
19	Chandran	50/M	98526	170	69	23.88	89	110/80	No	No	18	84	0.7	180	152	48	No	6	No
20	Murugan	35/M	98354	175	76	24.82	92	110/70	No	No	20	98	0.5	188	212	45	No	4	No
21	Kalaivanan	47/M	639	169	70	24.51	86	110/80	Yes	No	25	80	0.7	202	174	46	No	4.2	No
22	Vetrivel	45/M	971	170	70	24.22	92	110/80	No	Yes	24	90	0.6	180	140	42	No	3.5	No
23	Ramesh	28/M	19767	169	65	22.76	88	110/70	Yes	No	18	76	0.7	145	108	48	No	3.2	No
24	Suresh	29/M	761	174	70	23.12	86	110/70	Yes	No	25	70	0.4	180	140	50	No	3.6	No
25	Lakshmanan	48/M	5194	165	76	27.92	100	110/70	Yes	Yes	24	110	0.9	256	176	38	Yes	4.5	No
26	Kumar	36/M	79980	170	72	24.91	96	120/70	No	Yes	24	96	0.7	180	141	42	No	3.6	No
27	Ganesh	27/M	96941	176	69	22.28	94	110/70	Yes	No	25	90	0.6	190	138	40	No	3.1	No
28	Vignesh	43/M	96857	165	60	22.04	86	110/70	Yes	No	20	70	0.4	199	170	42	No	3.7	No
29	Ramasamy	49/M	71576	170	70	24.22	106	110/70	No	Yes	25	116	0.8	283	170	40	Yes	3.8	No
30	Thangavel	46/M	931	169	60	21.01	89	120/70	Yes	Yes	26	99	0.9	190	140	42	No	3.2	No
31	Selvi	33/F	96914	158	64	25.64	88	110/70	-	No	20	90	0.6	190	142	48	No	3.2	No
32	Chellammal	40/F	96902	160	62	24.22	86	110/70		Yes	24	86	0.7	210	138	50	No	3.8	No

33	Rasiammal	49/F	9691	155	59	24.56	84	110/80	-	Yes	36	90	0.9	180	152	52	No	3.6	No
34	Sarima	93/F	761	150	60	26.67	86	110/70	-	No	24	80	0.6	176	139	48	No	3.2	No
35	Fathima beevi	45/F	949	154	62	26.14	90	110/80	-	Yes	30	110	0.9	210	160	48	Yes	4.9	No
36	Padmavathy	29/F	92391	156	65	26.71	82	110/70	-	Yes	24	86	0.6	180	143	46	No	3.5	No
37	Latha	26/F	92390	160	66	25.78	86	110/80	-	Yes	20	90	0.6	210	156	48	No	4	No
38	Shanthi	38/F	92486	159	62	24.52	87	110/80	-	No	25	90	0.6	180	140	50	No	3.8	No
39	Valli	39/F	92383	160	65	25.39	86	110/70	-	No	24	80	0.7	213	143	48	No	3.9	No
40	Suganthi	31/F	92385	155	60	24.97	84	110/70	-	Yes	25	90	0.8	210	153	45	No	4.2	No
41	Muthammal	46/F	92381	100	62	25.68	86	110/70	-	Yes	24	70	0.6	183	140	48	No	3.8	No
42	Jansi	42/F	92382	170	75	25.95	84	110/80	-	Yes	26	90	0.7	190	143	42	No	6.1	Yes
43	Beevi	45/F	92383	165	59	21.67	88	110/70	-	No	25	110	0.7	256	183	45	Yes	6.2	Yes
44	Rani	38/F	92384	170	65	22.49	84	110/70	-	No	24	106	0.7	180	132	49	No	3.6	No
45	Susila	42/F	92387	159	64	25.32	85	120/80	-	No	29	110	0.6	190	193	55	No	3.9	No
46	Pushpa	45/F	92390	155	58	24.14	84	110/70	-	No	36	90	0.8	190	123	50	No	4.2	No
47	Sarkasi	32/F	92391	160	59	23.05	82	110/70		No	25	70	0.6	180	110	49	No	3.6	No
48	Pappammal	45/F	92392	165	64	23.51	86	110/76	-	No	20	120	0.5	240	163	48	Yes	4.9	No
49	Priyavathiri	29/F	92393	105	65	28.96	80	110/70	-	Yes	25	96	0.6	180	132	52	No	3.2	No
50	Rajeshwari	45/F	92994	165	60	22.04	84	110/70	-	Yes	26	76	0.8	190	110	48	No	3.6	No
51	Rajan	33/M	9531	170	74	25.61	96	110/70	No	No	25	80	0.6	180	143	48	No	3.6	No
52	Rengan	42/M	9532	180	76	23.46	90	120/80	Yes	Yes	24	96	0.8	210	130	42	No	8	Yes
53	Shanmugam	46/M	9537	165	65	23.88	88	110/80	No	Yes	20	70	0.6	193	120	40	No	3.6	No
54	Selvakumar	33/M	9534	160	59	23.05	90	110/70	No	No	25	73	0.6	153	125	48	No	3.5	No
55	Pragasam	32/M	9535	175	74	24.16	88	110/80	Yes	Yes	24	86	0.7	174	137	45	No	3.6	No
56	Balamurugan	28/M	9536	174	70	23.12	92	110/80	Yes	Yes	25	90	0.6	190	140	42	No	3.7	No
57	Ramajeyam	29/M	9537	175	70	22.86	91	110/80	Yes	Yes	22	76	0.6	180	142	46	No	3.5	No
58	Moses	36/M	9538	169	62	21.71	100	120/70	Yes	Yes	26	116	0.8	253	169	37	Yes	3.6	Yes
59	Ibrahim Ravuthar	46/M	9539	165	63	23.14	98	110/70	No	Yes	24	96	0.6	190	140	40	No	4.2	No
60	Anandhan	42/M	9540	170	65	22.49	99	110/70	No	Yes	25	90	0.5	180	146	42	No	3.6	No
61	Annasi	46/M	9541	172	68	22.99	86	110/80	Yes	No	24	86	0.4	176	136	40	No	3.2	No
62	Andiyappan	48/M	9542	170	65	22.49	88	110/70	No	No	28	90	0.6	210	150	42	No	7.2	Yes
63	Karthick	27/M	9543	172	63	21.3	84	110/76	Yes	Yes	32	86	0.5	190	102	48	No	3.5	No
64	Moorthy	28/M	9544	165	70	25.71	82	110/70	Yes	No	30	92	0.6	186	110	46	No	3.2	No
65	Krishnan	42/M	9546	169	72	25.21	90	120/80	Yes	Yes	28	102	0.7	210	138	42	No	3.9	No
66	Sethuraman	46/M	9547	168	79	27.99	92	120/80	No	No	29	8	0.6	253	190	37	No	7.2	Yes
67	Karmegam	38/F	9548	165	72	26.45	88	110/80	No	No	25	90	0.5	190	143	42	No	3.3	No
68	Muthu	29/M	9549	170	70	24.22	86	110/80	No	No	24	80	0.6	117	142	45	No	3.7	No

69	Thangavel	33/M	9550	175	66	21.55	90	120/80	Yes	Yes	24	99	0.5	180	138	46	No	3.8	No
70	Palanisamy	36/M	9551	175	60	20.59	90	120/80	No	Yes	22	96	0.7	190	112	40	No	3.7	No
71	Mookammal	46/F	9552	159	60	23.73	86	110/70	-	Yes	24	90	0.6	190	140	48	No	3.2	No
72	Chitradevi	37/F	9553	160	62	24.22	84	120/80	-	No	25	91	0.8	210	133	45	No	3.6	No
73	Radha	25/F	9554	162	58	22.1	82	110/70	-	No	26	70	0.7	183	143	50	No	4.1	No
74	Neelaveni	46/F	9555	165	65	23.88	85	120/80	-	Yes	32	76	0.8	195	102	52	No	5	No
75	Thangam	46/F	9556	155	60	24.97	87	120/70	-	Yes	36	87	0.9	180	176	48	No	3.6	No
76	Rajeswari	37/F	9557	162	69	26.29	84	110/70	-	No	24	90	0.5	153	110	55	No	3.1	No
77	Nagammal	48/F	9558	161	65	25.08	100	120/80	-	No	30	112	0.5	290	173	48	Yes	4.9	No
78	Rosi	22/F	9555	165	67	24.61	86	110/70	-	Yes	20	90	0.6	180	102	56	No	4.1	No
79	Nallammal	45/M	9560	159	59	23.34	86	120/80	-	Yes	22	92	0.9	210	163	55	No	3.8	No
80	Bhavani	43/F	5561	160	60	23.44	80	110/70	-	No	23	70	0.6	220	183	52	No	4.7	No
81	Lakhsmi	46/F	9562	159	62	24.52	84	110/70	-	No	26	86	0.6	180	140	54	No	4.1	No
82	Malarvili	23/F	9563	160	62	24.22	80	110/70	-	Yes	28	82	0.7	193	139	48	No	4.2	No
83	Jeyamani	38/F	9564	170	76	26.3	82	120/80	-	No	28	84	0.5	199	127	53	No	3.6	No
84	Backiyam	39/F	9565	159	72	28.48	89	110/70	-	Yes	26	116	0.7	253	183	45	Yes	4	No
85	Thangammal	49/F	9566	160	62	24.22	85	110/70	-	Yes	26	90	0.6	200	102	54	No	3.6	No
86	Rosathi	35/F	9567	160	59	23.05	84	120/80	-	Yes	28	92	0.6	149	167	55	No	3.7	No
87	Maheswari	29/F	9568	160	70	27.34	80	110/70	-	No	26	96	0.5	167	102	56	No	3.2	No
88	Velliammal	42/F	9569	155	62	25.81	90	120/80	-	Yes	27	98	0.5	189	108	52	No	3.6	No
89	Palaniammal	46/F	9570	157	63	25.56	85	110/70	-	No	20	100	0.4	210	125	50	No	3.8	No
90	Shenbagam	39/F	9572	160	60	23.44	83	110/70	-	Yes	25	90	0.5	210	145	52	No	5.1	No
91	Shanthi	23/F	9573	158	60	24.03	81	120/80	-	Yes	25	89	0.5	220	159	48	No	3.9	No
92	Eswari	28/F	9574	161	65	25.08	85	110/70	-	Yes	30	86	0.6	183	140	48	No	3.2	No
93	Raman	34/F	9575	170	66	22.84	90	120/70	No	Yes	26	76	0.5	210	163	42	No	4.1	No
94	Kumar	43/M	9576	170	67	23.18	94	110/70	Yes	No	27	85	0.4	147	168	40	No	4.1	No
95	Ramanathan	46/M	9577	165	80	29.38	92	110/70	Yes	Yes	29	182	0.8	280	175	34	Yes	4.9	No
96	Sankar	23/M	9578	175	76	24.82	93	110/80	Yes	Yes	30	36	0.8	212	143	46	No	3.8	No
97	Maharajan	29/M	9579	173	66	22.05	95	110/80	Yes	No	32	101	0.9	219	144	47	No	3.9	No
98	Mujahiv	42/M	9580	175	68	22.2	90	110/70	Yes	Yes	25	96	0.6	146	193	42	No	3.1	No
99	Sankar	23/M	9578	175	76	24.82	93	110/80	Yes	Yes	30	36	0.8	212	143	46	No	3.8	No
100	Velayu	39/M	9581	170	70	24.22	90	110/70	Yes	Yes	24	94	0.7	150	109	49	No	3.1	No